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

27 March 2015

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 referred to the **November 2014** meeting of the Advisory Committee on Chemicals Scheduling (ACCS#12);
- scheduling proposals referred to the **November 2014** joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS#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 25 September 2014 at https://www.tga.gov.au/consultation-invitation/consultation-invitation-public-comment-accs-acms-and-joint-accsacms-meetings-november-2014.

Redacted versions of the public submissions received in response to this invitation were published on **5 February 2015** at https://www.tga.gov.au/public-submissions-scheduling-matters.

Interim decisions

The delegates' interim decisions on recommendations by the ACCS#12 and the ACCS-ACMS#10 were published on 5 February 2015 at https://www.tga.gov.au/reasons-scheduling-delegates-interim-decisions-invitations-further-comment. These public notices 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.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes and interim decision on an application, the delegate may make a final decision 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 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), available at https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.

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. Further information, including links to the Poisons Standard on ComLaw, is available at https://www.tga.gov.au/publication/poisons-standard-susmp.

Glossary

Abbreviation	Name
ACCC	Australian Competition and Consumer Commission
ACCS	Advisory Committee on Chemicals Scheduling
ACMS	Advisory Committee on Medicines Scheduling
APVMA	Australian Pesticides and Veterinary Medicines Authority
CPS	Committee on Poisons Schedules
CAS	Chemical Abstract Service
CIR	Cosmetic Ingredient Review
DPSSC	Drugs and Poisons Scheduling Sub-Committee
EPA	Environmental Protection Authority (United States)
FDA	Food and Drug Administration (United States)
IMAP	Inventory Multi-tiered Assessment and Prioritisation
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
MOE	Margins Of Exposure
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NICNAS	National Industrial Chemicals Notification & Assessment Scheme

Abbreviation	Name
NOAEL	No observed adverse effect level
NOEL	No observable effect level
OCS	Office of Chemical Safety
PEC	Priority existing chemical
PSC	Poisons Schedule (Standing) Committee
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SPF	*Scheduling Policy Framework for Medicines and Chemicals* https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals
TGA	Therapeutic Goods Administration

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

1. Scheduling proposals referred to the November 2014 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #12)

1.1. SUMMARY OF FINAL DECISIONS

Substance	Final Decision
1,2-Benzendicarboxylic acid, bis(2-methoxyethyl) ester (DMEP) and 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (DiBP)	**New Appendix C/Schedule 10 entry** DI(METHYLOXYETHYL) PHTHALATE for cosmetic use. **New Appendix C/Schedule 10 entry** DIISOBUTYL PHTHALATE for cosmetic use. Implementation date – 1 June 2015
1,4-Benzenediamine, 2-nitro	Pending
Alkoxyethanols (C1-C2) and their acetates	**New Schedule 7 entries** 2-METHOXYETHANOL and its acetates **except** in preparations containing 0.5 per cent or less of 2-methoxyethanol. 2-ETHOXYETHANOL and its acetates **except** in preparations containing 0.5 per cent or less of 2-ethoxyethanol. **New Appendix F, Part 3 entries** 2-METHOXYETHANOL – warning statement 77, safety directions 1,4,8 2-ETHOXYETHANOL - warning statement 77, safety directions 1,4,8 Implementation date – 1 June 2015
Benzidine-congener based dyes	**New Schedule 7 entry** BENZIDINE-CONGENER (3,3'-disubstituted) AZO DYES. Implementation date – 1 June 2015

Substance	Final Decision
C. I. Acid black 29	**Amendment to Schedule 7 entry** BENZIDINE-BASED AZO DYES add C.I Acid Black 29 to list of substances covered by this entry Implementation date – 1 June 2015
Fenpyrazamine	**New Schedule 5 entry** FENPYRAZAMINE except in preparations containing 40 per cent or less of fenpyrazamine Implementation date – 1 June 2015
Fluopyram	**New Schedule 5 entry** FLUOPYRAM **except** in preparations containing 50 per cent or less of fluopyram Implementation date – 1 June 2015
Formaldehyde donors	Pending
Methylated spirit(s)	Pending
Methyl Ethyl Ketone Oxime	**Amendment to Schedule 6 entry** METHYL ETHYL KETONE OXIME **except:** a. in viscous silicone adhesives or viscous silicone sealants containing 2.5% or less of methyl ethyl ketone oxime; or b. in other preparations containing 1 per cent or less of methyl ethyl ketone oxime. Implementation date – 1 June 2015

1.2. 1,2-Benzendicarboxylic acid, bis(2-methoxyethyl) ester (DMEP) and 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (DiBP)

Scheduling proposal

The chemicals scheduling delegate (the delegate) referred the following scheduling proposal for consideration by the Advisory Committee on Chemicals Scheduling (ACCS):

- To create new Schedule entries for 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester (Di(methoxyethyl) phthalate or DMEP) and 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (Diisobutyl phthalate or DiBP) in Appendix C.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In August 2014, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Priority Existing Chemicals (PEC) assessment programme for 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester (Di(methoxyethyl) phthalate or DMEP) and Inventory Multi-tiered Assessment Prioritisation (IMAP) programme for 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (Diisobutyl phthalate or DiBP), referred the following proposal to be considered by the delegate:

- A proposal to create new entries for 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester (Di (methyoxyethyl) phthalate or DMEP) and 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (Diisobutyl phthalate or DiBP) in Appendix C.

The reasons for the request were:

- Adverse effects on fertility and development (mediated by testicular toxicity, abnormal spermatogenesis, reduced pup weight, and altered sexual differentiation).

- The C4-6 transitional phthalate group of chemicals which include 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester can cause anaemia (repeated dose toxicity).

- 1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl) ester is classified as hazardous under the Hazardous Substances Information System (HSIS) with the risk phrases Repro Cat 2 (R61 'May cause harm to the unborn child'); Repro Cat 3 (R62 'Possible risk of impaired fertility').

NICNAS recommended that the chemicals be listed in Appendix C to limit the potential exposure of the public, including young children, to the chemical from possible use in cosmetics.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that, the NICNAS referral seeks a restrictive scheduling to regulate the use of DMEP and DiMP in cosmetic products. The Scheduling Policy Framework (SPF) recommends that the delegate seek advice from an advisory committee for such restrictive scheduling actions.

The delegate asked the ACCS the following questions:

- The related phthalate esters diethylphthalate (DEP) and dimethylphthalate (DMP) are listed in Appendix C to restrict use in sunscreens, personal insect repellents or body lotions, while dibutylphthalate (DBP) and diethylhexyl phthalate (DEHP) listings in Appendix C restrict use in cosmetic products. Are the toxicity profile and risk assessment relating to cosmetic use of DMEP and DiBP sufficiently similar to these other phthalates to warrant a parallel entry for them both in Appendix C? Note that this proposal is pre-emptive, in that there is no evidence that either DiBP or DMEP is currently used in cosmetic products in Australia or overseas.

- Should the parallel entry specify use in cosmetics, to cover a broader range of products, and is there any basis for setting an exemption cut-off (as for DEP and DMP)?

- Which names should be used for the proposed listings in Appendix C? The NICNAS IMAP report lists the names diisobutyl phthalate and di-(methoxyethyl) phthalate as possible names for

DiBP and DMEP, respectively. This nomenclature may be more consistent with that used for existing Appendix C entries for phthalate esters.

- Given that the current Appendix C entries for DMP and DEP appear to have been initially developed for personal insect repellents after consideration of their referral from the APVMA registration process, and subsequently extended to sunscreens and body lotions after consideration of a NICNAS evaluation, is there a case for foreshadowing an amendment to the DMP and DEP entries to encompass all cosmetic products?

Substance summary

Please refer to the NICNAS PEC assessment report for *Di(methoxyethyl) phthalate (DMEP)* and the NICNAS IMAP human health Tier II assessment report for *C4-6 side chain transitional phthalates*.

The PEC report is publicly available on the NICNAS website http://www.nicnas.gov.au/chemical-information/pec-assessments.

The IMAP assessment report is publicly available on the NICNAS website http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1126.

Scheduling status

1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester (Diisobutyl phthalate or DiBP) and 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester (Di(methyoxyethyl) phthalate or DMEP) are not specifically scheduled.

Scheduling history

Neither 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (DiBP) nor 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester (DMEP) have been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One submission was received that tentatively supports the inclusion of DMEP and DiPB for cosmetic use in Appendix C.

Summary of ACCS advice to the delegate

The committee recommended that a new Appendix C be created for cosmetic preparations containing Di(methoxyethyl) phthalate and Diisobutyl phthalate.

The committee supported the implementation date of 1 June 2015.

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:

- Systemic and reproductive toxicity consistent with related transitional phthalates warrant restrictions.

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*;
- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate accepts the advice from the ACCS and agrees to create new entries in Appendix C/Schedule 10 for cosmetic preparations containing Di(methoxyethyl) phthalate and Diisobutyl phthalate. The decision is based on the NICNAS assessment that there is an inadequate safety margin associated with their potential use in cosmetic products and it is consistent with previous scheduling actions to restrict the use of other phthalate esters with comparable reproductive toxicity potential.

The delegate agrees with the implementation date 1 June 2015.

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

Public submissions on the interim decision

One public submission was received. The submission noted they had previously provided comments on this item, but had no further comment to make in response to the interim decision.

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.

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Appendix c/Schedule 10 – New entry

DI(METHYLOXYETHYL) PHTHALATE for cosmetic use.

Appendix c/Schedule 10 – New entry

DIISOBUTYL PHTHALATE for cosmetic use.

1.3. Alkoxyethanols (C1-C2) and their acetates

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the ACCS:

To develop separate entries for:

- 2-methoxyethanol (Inventory Multi-tiered Assessment and Prioritisation (IMAP) report for *alkoxyethanols (C1-C2) and their acetates*),
- 2-ethoxyethanol (IMAP report for *alkoxyethanols (C1-C2) and their acetates*),

- 2-(1-methylethoxy)ethanol (IMAP report for *2-(1-methylethoxy)ethanol and its acetate*),
- 2-butoxyethanol (IMAP report for *ethanol, 2-butoxy-, acetate*), and
- 2-propoxyethanol (IMAP report for *ethanol, 2-propoxy*), along with their acetates.

These proposals require consideration of changes to the exemption cut-offs for the Schedule 6 entries, and the need for separate entries in Appendices E, F and I.

There is currently a generic entry in Schedule 6 for ETHYLENE GLYCOL MONOALKYL ETHERS and their ACETATES. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) IMAP programme has reviewed a number of chemicals in this class and recommended that separate entries be created for selected chemicals in this class. In November 2013, the delegate decided to separately list a similar substance namely 2-hexyloxyethanol. This decision was based on an outcome of the July 2013 ACCS meeting.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In August 2014, NICNAS, under its IMAP programme, referred the following proposal to be considered by the delegate:

- To separately list 2-methoxyethanol, 2-ethoxyethanol, 2-(1-methylethoxy)ethanol, 2-butoxyethanol and 2-propoxyethanol and their acetates in Schedule 6.

NICNAS suggested that any review of the substance entry in the Poisons Standard should form a part of a review of the entries for all ethylene glycol monoalkyl ethers and their acetates.

The reasons for the request were:

At present, the chemicals fall within the scope of the listing of ethylene glycol monoalkyl ethers in Schedule 6 of the SUSMP for preparations containing more than 10 % of glycol ether. However, the health effects of the members in this class of chemicals vary significantly and a separate listing for the chemicals in this group might be more appropriate.

- Whilst the chemicals meet the criteria for Schedule 6, given the critical health effects identified, a lower concentration cut-off (than the current 10%) might be appropriate for some substances, and a higher concentration cut-off level may be more appropriate for others.
- Physiologically based pharmacokinetic (PBPK) modelling suggests that humans could experience toxic effects at concentration levels lower than those observed in animals.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that the SPF suggests that all re-scheduling proposals be referred to the relevant advisory committee.

The delegate asked the ACCS the following questions:

- The current generic Schedule 6 entry ETHYLENE GLYCOL MONOALKYL ETHERS and their ACETATES would cover the five chemicals referred by NICNAS for consideration of replacement with specific entries. Are there sufficient similarities or differences in their toxicity profiles that they could warrant separate Schedule 6 entries and concentration cut-off levels to exempt (currently 10%) from scheduling?

- Is there a need to develop separate entries in Schedule 6, as well as Appendices E, F and I as the delegate recommended at the July 2013 meeting for 2-hexyloxyethanol, with different concentration cut-off levels to exempt from scheduling for each substance?
- Note that the NICNAS IMAP reports for 2-butoxyethanol, 2-propoxyethanol and 2-methylethyloxyethanol suggest that concentrations higher than 10% can be used safely, is this a justification for separate Schedule 6 entries with higher cut-off levels?
- What weight should be given to the claim in the NICNAS report for 2-methoxyethanol and 2-ethoxyethanol that physiologically based pharmacokinetic (PBPK) modelling suggests that humans could experience toxic effects at concentration levels lower than those observed in animals?
- Does the more recent toxicity data on 2-methoxyethanol and 2-ethoxyethanol reviewed in the NICNAS report suggest that a cut-off at 10% is no longer appropriate, and that a lower concentration cut-off level to exempt from scheduling should be considered for these two chemicals?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report on *alkoxyethanols (C1-C2) and their acetates*, *2-(1-methylethoxy)ethanol and its acetate*, *ethanol, 2-butoxy* and *ethanol, 2-propoxy*.

These reports are publicly available on the NICNAS website:

- *alkoxyethanols (C1-C2) and their acetates* (2-Methoxyethanol and 2-ethoxyethanol) http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1100
- *2-(1-methylethoxy)ethanol and its acetate* http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=197
- *Ethanol, 2-butoxy acetate* http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=194
- *Ethanol, 2-propoxy-* http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=79

Scheduling status

2-Methoxyethanol, 2-ethoxyethanol, 2-(1-methylethoxy)ethanol, 2-butoxyethanol and 2-propoxyethanol and their acetates are not specifically scheduled.

These substances belong to the chemical class of ethylene glycol monoalkyl ethers. Ethylene glycol monoalkyl ethers and their acetates are listed in Schedule 6 and Appendices E, F and I.

Another similar substance, namely hexyloxyethanol or 2-hexyloxyethanol is listed in Schedule 6 and Appendices E, F and I.

Scheduling status of ethylene glycol monoalkyl ethers

Schedule 6

ETHYLENE GLYCOL MONOALKYL ETHERS and their ACETATES, **except**:

a. when separately specified in these Schedules; or

b. in preparations containing 10 per cent or less of such substances.

Appendix E, Part 2

Poison	Standard statements
Ethylene glycol monoalkyl ethers and their acetates **except** when separately specified	A,G3,E2,S1

Appendix F, Part 3

Poison	Warning statements	Safety direction
Ethylene glycol monoalkyl ethers and their acetates **except** when separately specified		1, 4, 8

Appendix I

The Second Schedule

Substance	Proportion
Ethylene glycol monoalkyl ethers and their acetates except when separately specified	more than 10 per cent by vol

Scheduling status of hexyloxyethanol

Schedule 6

HEXYLOXYETHANOL **except** in preparations containing 10 per cent or less of hexyloxyethanol.

Appendix E, Part 2

Poison	Standard statement
Hexyloxyethanol	A,G3,E2,S1

Appendix F, Part 3

Poison	Warning statement	Safety direction
Hexyloxyethanol	2	1, 4, 8

Appendix I

The Second Schedule

Substance	Proportion
Hexyloxyethanol	more than 10 per cent by vol

Scheduling history

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, haematological effects and were toxic at inhalation levels at the 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 more 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 November 2013, the delegate, based on the ACCS advice, decided to create a separate schedule entry for hexyloxyethanol with a cut-off level to exempt from scheduling for preparations containing 10 per cent of less of hexyloxyethanol. The delegate also decided to create new Appendices E, F and I entries specifically for hexyloxyethanol. The delegate's decision was based on the fact that hexyloxyethanol's toxicity profile was different from the chemical class ethylene glycol monoalkyl ethers.

Pre-meeting public submissions

Two submissions were received.

One submission noted that this schedule entry applies to a wide range of chemicals that, while chemically related (i.e. derivatives, chemically speaking), are not toxicologically similar (i.e. should not be considered derivatives for toxicological purposes). The submission requested that the ACCS consider limiting the schedule 6 entry to short alkyl chain glycol ethers, and also consider limiting the schedule entry to compounds with 1 mole alkyl ethers i.e. ethylene glycol monoalkyl ethers, excluding derivatives.

The second submission noted that methoxyethanol and ethoxyethanol are used in a number of topical cosmetic products at low concentrations with no reported safety issues they are aware of. The submission requested that if a Schedule 6 entry is adopted, the committee and delegate exempt cosmetic products containing methoxyethanol and ethoxyethanol in low concentrations from scheduling.

Summary of ACCS advice to the delegate

The committee recommended that 2-methoxyethanol and its acetates and 2-ethoxyethanol and its acetates, based on their reproductive toxicity potential, be listed in Schedule 7.

The committee recommended that 2-(1-methylethoxy) ethanol, 2-propoxyethanol and their acetates do not require a separate schedule listing.

The committee supported the implementation date of 1 June 2015.

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

- reproductive toxicity potential.

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*;
- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

For some time, the scheduling of this group of alkoxyethanols has been covered by the generic Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates. More recently, as a results of NICNAS IMAP evaluations, some individual members have been referred for consideration of whether separate entries (with possibly different exemption cut-offs) would be more appropriate for some members of this class of compound, given the differences in their toxicity profile as the alkyl side chain is lengthened. The separate listing of butoxyethanol and hexyloxyethanol in Schedule 6 (with the same 10% exemption cut-off) is an example of these more recent scheduling reconsiderations.

The current advice from the ACCS is that the toxicity profiles of 2-butoxyethanol, 2-propoxyethanol and 2- methylethyloxyethanol are consistent with the listing in Schedule 6 and that they are adequately covered by the current generic entry (noting that butoxyethanol already has a separate listing in Schedule 6). Despite some evidence in the NICNAS IMAP reports suggesting that, for these specific alkoxyethanols, concentrations higher than 10% can be used safely, the ACCS did not recommend raising the current 10% cut-off to exempt. The delegate accepts the ACCS advice and makes no recommendation for a separate listing in Schedule 6 for 2-propoxyethanol and 2-methylethyloxyethanol.

In the case of methoxyethanol and ethoxyethanol (and their acetates), the ACCS made a different recommendation. On the basis of their reproductive and developmental toxicity potential, and NICNAS assessment that product concentrations below 10% could result in unacceptable Margin of Safety estimates, the ACCS recommended that both be listed in Schedule 7, with no cut-off to exempt or to a lower Schedule. Given the serious nature of their toxicity profile and the fact that both substances are listed by the European Chemicals Agency (ECHA) as '*substances of very high concern*', the delegate accepts that a primary listing in Schedule 7 is more appropriate than the existing coverage by the generic Schedule 6 entry. However, the delegate has concerns that the ACCS did not recommend any cut-off to exempt or to a lower schedule. This could have significant regulatory impact on existing products. While the NICNAS report suggests there are no known uses of methoxyethanol, ethoxyethanol or their acetates in Australia, an industry submission noted the potential for them to be present at very low concentrations (or as impurities?) in some cosmetic

products. In the absence of any definitive advice from the ACCS on a suitable cut-off from the proposed Schedule 7 listing (substances in Schedule 7 are not eligible for the generic 10 ppm exemption in Part 1 of the SUSMP), the delegate proposes to include an exemption clause in the Schedule 7 entry at the REACH maximum of 0.5%.

The ACCS considered the need for Appendix F warning Statements for products covered by the Schedule 7 listing, but ultimately did not put a recommendation. Nor did the ACCS address the need to an entry in Appendix J. The delegate proposes that, in addition to the standard Warning Statements 1,4 and 8 applied to all ethylene glycol monoalkyl ethers, there is a need to also specify WS 77 (WARNING – may cause birth defects) for any products captured by the Schedule 7 entry.

The delegate agrees with the implementation date 1 June 2015.

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

Public submissions on the interim decision

One public submission was received. The submission noted they had previously provided comments on this item, but had no further comment to make in response to the interim decision.

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.

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 7 - New entries

2-METHOXYETHANOL and its acetates **except** in preparations containing 0.5 per cent or less of 2-methoxyethanol.

2-ETHOXYETHANOL and its acetates **except** in preparations containing 0.5 per cent or less of 2-ethoxyethanol.

Appendix F, Part 3 – New entries

Poison	Warning statements	Safety direction
2-METHOXYETHANOL and its acetates	77	1,4,8
2-ETHOXYETHANOL and its acetates	77	1,4,8

1.4. Benzidine-congener based dyes

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the ACCS:

- To insert a new entry for benzidine-congener-based dyes in the SUSMP, to prohibit their sale, supply and use in dyes for home use.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In August 2014, NICNAS, under its IMAP programme, referred the following proposal to be considered by the delegate:

- A proposal to insert a new entry to the SUSMP for various benzidine-congener-based dyes to prohibit their sale, supply and use in dyes for home use.

The reasons for the request were:

- The chemicals are both genotoxic and carcinogenic in animals. The benzidine-congener metabolites are reasonably anticipated to be potent human carcinogens; this is also considered to be the case for the non-metalised dyes given that:
  - the incidence of malignant tumours observed following exposure to Acid Red 114 and Direct Blue 15 was also similar to that observed following exposure to 3,3'-DMB and 3,3'-DMOB; and
  - the amount of free benzidine-congener detected in animals was equivalent to that observed following an equimolar dose of benzidine-congener.
- Whilst metal chelation appears to render the chemicals more inert towards metabolism, based on data for C.I. Direct Blue 218, this does not completely eliminate the azo reduction and carcinogenicity potential of the chemicals.

NICNAS recommended that the chemicals be scheduled to prohibit their sale, supply and use in dyes for home use.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that, advice was requested from the ACCS to determine whether a Schedule 7 entry for benzidine-congener-based dyes should be added to the current Schedule 7 entry for BENZIDINE-BASED AZO DYES, or a new separate entry be created in Schedule 7.

The NICNAS IMAP programme has reviewed a number of diazotized benzidine derivatives likely to be a component of dyes and stains and found that the toxicological profile of these benzidine-based azo dyes is consistent with the SPF criteria for listing in Schedule 7 (based on their mutagenicity and carcinogenicity profile and ability to be metabolised to benzidine, a known human carcinogen). Scheduling recommendations from the November 2013 ACCS meeting resulted in eleven of these substances being listed in Schedule 7.

The Delegate asked the ACCS the following questions:

- The toxicological profile of the 66 dyes listed in the NICNAS IMAP report is based on read-across from a few related dyes, and the assumption that all will be metabolised *in vivo* to benzidine or its congeners. Is there sufficient evidence to conclude that they represent the same hazard profile as other benzidine-based azo dyes currently listed in Schedule 7, and therefore warrant addition to that entry?
- Should all 66 of the listed benzidine-congener-based azo dyes (and their CAS numbers) be simply added to the list of dyes currently captured by the generic Schedule 7 entry for BENZIDINE-BASED AZO DYES, or should they be listed under a separate schedule entry?

- What weight should be given to 'the reasonably anticipated to be human carcinogens' classification for the three congeners expected to be their metabolites (3,3'-DCB, 3,3'-DMOB and 3,3'-DMB) for the NICNAS assessment report for these chemicals), as opposed to the 'known human carcinogen' classification for benzidine?

- What weight should be given to the disclosure in the NICNAS IMAP report that these dyes are being phased out internationally and that there may be no current uses in Australia, other than the possibility that some of them might be present in imported textiles and fabrics? Are there likely to be other products available in the retail market that may contain these dyes?

- Should the schedule 7 wording be limited to dyes available to the general public for home use, or should there be blanket coverage of all products where the dyes have been used?

- Is the regulatory impact of adding these benzidine-congener-based dyes to Schedule 7 likely to be similar, or greater than, the effects on products covered by the current Schedule 7 listing of benzidine-based azo dyes?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *Selected Benzidine-Congener-Based Dyes*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1022.

Scheduling status

Benzidine-congener-based dyes are not specifically scheduled.

Benzidine based azo dyes are listed in Schedule 7.

Schedule 7

BENZIDINE-BASED AZO DYES being:

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

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

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

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

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

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

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

- Direct Green 1. 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-3-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-6-(phenylazo)-, disodium salt. CAS No. 3626-28-6
- Direct Green 6. 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-6-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-3-[(4-nitrophenyl)azo]-, disodium salt. CAS No. 4335-09-5
- Direct Red 28 (Congo Red). 1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[4-amino-, disodium salt. CAS No. 573-58-0
- Direct Red 37. 1,3-Naphthalenedisulfonic acid, 8-[[4'-[(4-ethoxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-7-hydroxy-, disodium salt. CAS No. 3530-19-6

Scheduling history

Benzidine-congener-based dyes are not specifically scheduled.

The following is the scheduling history of benzedine-based azo dyes.

In April 2014, the delegate, based on ACCS advice, made a decision to list 11 benzidine-based dyes in Schedule 7. The delegate indicated that inclusion of benzidine-based dyes in Appendix C is not the most appropriate way of regulating the use of these substances. The delegate also noted that some of the dyes may have use as laboratory and analytical reagents. While there are stringent existing controls under Model Work Health and Safety legislation, and industry advises that they have been largely phased out of many uses, their carcinogenic potential, via conversion to benzidine (a known human carcinogen), indicates they should not be used in products available in the domestic market.

Pre-meeting public submissions

No submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that a new Schedule 7 entry be created for benzidine-congener (3,3'-disubstituted) azo dyes.

The committee supported the implementation date of 1 June 2015.

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:

- Concerns about the potential carcinogenic and reproductive affects.

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*;

- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that a new Schedule 7 generic entry be created for benzidine-congener (3,3'-disubstituted) azo dyes. The scheduling proposal complements previous decisions to list in Schedule 7 some azo dyes that can be metabolized to benzidine, a known human carcinogen. While the three congeners expected to be their metabolites (3,3'-DCB, 3,3'-DMOB and 3,3'-DMB) are classified as *'reasonably anticipated to be human carcinogens'*, rather than the *'known human carcinogen'* classification for benzidine, the ACCS considers that their carcinogenic potential warrants similar restrictive scheduling. The delegate notes that the NICNAS report lists 66 substances that fit the generic description. Rather than list these substances individually by name (as in the current Schedule 7 listing for BENZIDINE-BASED AZO DYES), the delegate notes that there is precedent for a generic entry to capture a group of substances with similar hazard characteristics and that this is a more pragmatic approach than listing the 66 individual substances included in the NICNAS report.

The delegate agrees with the implementation date 1 June 2015.

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

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

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 7 – New entry

BENZIDINE-CONGENER (3,3'-disubstituted) AZO DYES.

1.5. C. I. Acid black 29

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the ACCS:

- To create a new entry for C. I. Acid Black 29 in Schedule 7.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015 /1 October 2015 /1 February 2016.

In August 2014, NICNAS, under its IMAP programme, referred the following proposal to be considered by the delegate:

- To create a new entry for C. I. Acid Black 29 in Schedule 7, consistently with other benzidine-based dyes.

The reasons for the request were:

- Systemic long-term effects including carcinogenicity, reproductive toxicity and developmental toxicity.
- Benzidine based-dyes have been shown to be metabolised to benzidine, a known human carcinogen.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that, the NICNAS IMAP program has reviewed a number of diazotized benzidine derivatives likely to be a component of dyes and stains. The toxicological profile of these benzidine-based azo dyes is consistent with the Scheduling Policy Framework's (SPF) criteria for listing in Schedule 7 (based on their mutagenicity and carcinogenicity profile and ability to be metabolised to benzidine, a known human carcinogen). The scheduling recommendations from the November ACCS meeting resulted in eleven benzidine-based azo dyes being listed in Schedule 7. Further advice of the ACCS was requested to determine whether CI Acid Black 29 should be added to the current Schedule 7 entry for BENZIDINE-BASED AZO DYES.

The delegate asked the ACCS the following questions:

- The NICNAS IMAP report contains no direct toxicological information on CI Acid Black 29. Its toxicological profile is based on read-across from related dyes and the assumption that it, too, is metabolised *in vivo* to benzidine. Is there sufficient evidence to conclude that it represents the same hazard profile as other benzidine-based azo dyes listed in Schedule 7, and therefore warrants inclusion in that entry?
- Should CI Acid Black 29 (and its CAS number) be simply added to the list of dyes currently captured by the generic Schedule 7 entry for BENZIDINE-BASED AZO DYES, or should it be listed under a separate schedule entry?
- What weight should be given to the disclosure in the NICNAS IMAP report that these dyes are being phased out internationally and that there may be no current uses in Australia, other than the possibility that CI Black 29 might be present in imported textiles and fabrics?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *C. I. Acid Black 29*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1252.

Scheduling status

C.I. Black 29 is not specifically scheduled.

Eleven benzidine-based azo dyes are listed in Schedule 7.

Schedule 7

BENZIDINE-BASED AZO DYES being:

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

- Acid Red 85 (Acid Fast Red A). 1,3-Naphthalenedisulfonic acid, 7-hydroxy-8-[[4'-[[4-[[(4-methylphenyl)sulfonyl]oxy]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-, disodium salt. CAS No. 3567-65-5
- Direct Black 38. 2,7-Naphthalenedisulfonic acid, 4-amino-3-[[4'-[(2,4-diaminophenyl)azo][1,1'-biphenyl]-4-yl]azo]-5-hydroxy-6-(phenylazo)-, disodium salt. CAS No. 1937-37-7
- Direct Blue 2. 2,7-Naphthalenedisulfonic acid, 5-amino-3-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-4-hydroxy-, trisodium salt. CAS No. 2429-73-4
- Direct Blue 6. 2,7-Naphthalenedisulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[5-amino-4-hydroxy-, tetrasodium salt. CAS No. 2602-46-2
- Direct Brown 2. 5-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxy- benzoic acid disodium salt. CAS No. 2429-82-5
- Direct Brown 95. Cuprate(2-), [5-[[4'-[[2,6-dihydroxy-3-[(2-hydroxy-5-sulfophenyl)azo]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxybenzoato(4-)]-, disodium salt. CAS No. 16071-86-6
- Direct Green 1. 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-3-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-6-(phenylazo)-, disodium salt. CAS No. 3626-28-6
- Direct Green 6. 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-6-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-3-[(4-nitrophenyl)azo]-, disodium salt. CAS No. 4335-09-5
- Direct Red 28 (Congo Red). 1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[4-amino-, disodium salt. CAS No. 573-58-0
- Direct Red 37. 1,3-Naphthalenedisulfonic acid, 8-[[4'-[(4-ethoxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-7-hydroxy-, disodium salt. CAS No. 3530-19-6

Scheduling history

C.I. Acid black 29 is not specifically scheduled.

The following is the scheduling history of benzedine-based azo dyes.

In April 2014, the delegate, based on ACCS advice, made a decision to list 11 benzidine-based dyes in Schedule 7. The delegate indicated that inclusion of benzidine-based dyes in Appendix C is not the most appropriate way of regulating the use of these substances. While there are stringent existing controls under Model Work Health and Safety legislation, and industry advises that they have been largely phased out of many uses, the delegate also noted that some of the dyes may have use in laboratory and analytical reagents, but that their carcinogenic potential, via conversion to benzidine (a known human carcinogen), indicates they should not be used in products available in the domestic market.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that the current Schedule 7 BENZIDINE-BASED AZO DYES entry be amended to include C.I. Acid black 29.

The committee supported the implementation date of 1 June 2015.

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:

- Concerns about the potential carcinogenic and reproductive affects.

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*;
- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate notes that a number of benzidine-based azo dyes were listed in Schedule 7 as an outcome of advice from the February 2014 meeting of the ACCS. The listed dyes warrant stringent controls because of their carcinogenic potential via conversion to benzidine (a known human carcinogen). The delegate therefore accepts ACCS advice that CI Acid Black 29 shares the carcinogenic potential of the already listed benzidine-based azo dyes and that it should be added to the list of such dyes in the current Schedule 7 listing.

The delegate agrees with the implementation date 1 June 2015.

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

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.

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 7 - Amendment

BENZIDINE-BASED AZO DYES being:

- 2,2'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[N-(4-chlorophenyl)-3-oxobutanamide], CAS No. 94249-03-3
- Acid Red 85 (Acid Fast Red A). 1,3-Naphthalenedisulfonic acid, 7-hydroxy-8-[[4'-[[4-[[(4-methylphenyl)sulfonyl]oxy]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-, disodium salt. CAS No. 3567-65-5
- C. I. ACID BLACK 29. CAS No. 12217-14-0
- Direct Black 38. 2,7-Naphthalenedisulfonic acid, 4-amino-3-[[4'-[(2,4-diaminophenyl)azo][1,1'-biphenyl]-4-yl]azo]-5-hydroxy-6-(phenylazo)-, disodium salt. CAS No. 1937-37-7
- Direct Blue 2. 2,7-Naphthalenedisulfonic acid, 5-amino-3-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-4-hydroxy-, trisodium salt. CAS No. 2429-73-4
- Direct Blue 6. 2,7-Naphthalenedisulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[5-amino-4-hydroxy-, tetrasodium salt. CAS No. 2602-46-2
- Direct Brown 2. 5-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxy- benzoic acid disodium salt. CAS No. 2429-82-5
- Direct Brown 95. Cuprate(2-), [5-[[4'-[[2,6-dihydroxy-3-[(2-hydroxy-5-sulfophenyl)azo]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxybenzoato(4-)]-, disodium salt. CAS No. 16071-86-6
- Direct Green 1. 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-3-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-6-(phenylazo)-, disodium salt. CAS No. 3626-28-6
- Direct Green 6. 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-6-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-3-[(4-nitrophenyl)azo]-, disodium salt. CAS No. 4335-09-5
- Direct Red 28 (Congo Red). 1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[4-amino-, disodium salt. CAS No. 573-58-0
- Direct Red 37. 1,3-Naphthalenedisulfonic acid, 8-[[4'-[(4-ethoxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-7-hydroxy-, disodium salt. CAS No. 3530-19-6

1.6. Fenpyrazamine

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the ACCS:

- To create a Schedule 5 entry for fenpyrazamine.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In August 2014, the Office of Chemicals Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Authority (APVMA), referred the following proposal to be considered by the delegate:

- A proposal to create a new Schedule 5 entry for fenpyrazamine.

The reasons for the request were that the chemical:

- has low oral toxicity in rats (LD_{50} >2000 mg/kg bw, no deaths);
- has low dermal toxicity in rats (LD_{50} >2000 mg/kg bw, no deaths);
- has low inhalational toxicity in rats (LC_{50} >4840 mg/m^3, no deaths, although the study was of reduced regulatory value based on exceedance of the mass median aerodynamic diameter (MMAD));
- is not a skin or eye irritant in rabbits; and
- is not a skin sensitiser in guinea pigs.

The toxicity profile of the preparation containing 400 g/L of fenpyrazamine was similar to the technical grade active constituent (TGAC), except for the inhalational toxicity. The inhalational toxicity value of the preparation containing 400 g/L of fenpyrazamine is >5612 mg/m^3, no deaths; and the TGAC's inhalational toxicity value is >4840 mg/m^3, no deaths.

The OCS evaluation report noted that in the current context of the toxicological profile of fenpyrazamine, the OCS has based its Schedule 5 recommendation primarily on the SPF Schedule 5 factor *"the substance has a low health hazard"*, but that the delegate may wish to consider whether the toxicological profile of fenpyrazamine was of sufficiently low health hazard, and whether there was sufficient public benefit, for a positive listing in Appendix B. Noting the uncertainty surrounding some of the findings in the two-year rat chronic/carcinogenicity study, from a cautionary principle approach, a Schedule 5 listing may be more appropriate.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that the scheduling application was sufficiently complex to require advice from the ACCS.

The delegate asked the ACCS the following questions:

- To what extent is the toxicological profile of fenpyrazamine similar to other pyrazole fungicides (penflufen sedaxane), whose primary listing is currently in Schedule 5?
- Despite the OCS conclusion, based on Mode of Action (MoA) analysis, that the carcinogenic response (high dose hepatocellular carcinomas and other tumours; no evidence of genotoxicity) seen in the 2-year rat study is unlikely to be relevant to humans, does the ACCS support the OCS recommendation that fenpyrazamine be listed in Schedule 5?
- Alternatively, does the overall low toxicity profile suggest that listing in Appendix B may be appropriate?

Substance summary

Fenpyrazamine is a non-systemic fungicide belonging to the pyrizole chemical family. Although the compound is classified as non-systemic, limited translocation in plants was observed. Fenpyrazamine shows its fungicidal activity through inhibition of germ tube elongation and mycelium elongation. The exact biochemical mechanism of the fungicidal activity is not clarified[1].

[1] Reasoned opinion on the modification of the existing MRLs for fenpyrazamine in apricots, cherries, peaches and plums. European Food Safety Authority. Accessed on 1 September 2014. Available at http://www.efsa.europa.eu/en/efsajournal/doc/3619.pdf

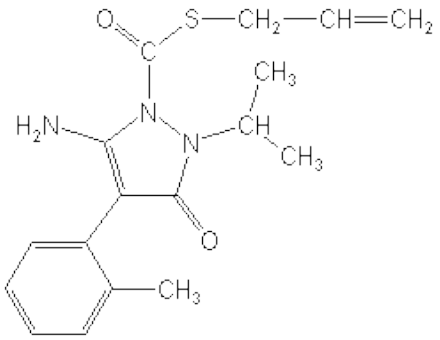

Figure 1. Structure of fenpyrazamine

Acute toxicity

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

Toxicity	Species	Fenpyrazamine	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (no deaths)	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (no deaths)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	> 4840 (no deaths)	Low toxicity
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Non-irritant	
Skin sensitisation (Guinea Pig Maximisation Test)	Guinea pig	Non-sensitiser	

The acute toxicity end-points a preparation containing 400 g/L of fenpyrazamine listed in the below table.

Toxicity	Species	Preparations containing 400g/L of fenpyrazamine	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (no deaths)	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (no deaths)	Low toxicity
Acute inhalational toxicity	Rat	> 5612 (no deaths)	Low toxicity

Toxicity	Species	Preparations containing 400g/L of fenpyrazamine	SPF classification
LC_{50} (mg/m^3/4h)			
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Non-irritant	
Skin sensitisation (Buehler method)	Guinea pig	Non-sensitiser	

Repeated dose toxicity

In repeat-dose toxicity studies, the most sensitive species was the rat, with some common toxicology endpoints in all species (test substance related and dose dependent reduction in food consumption, lower body weight and decreased body weight gain), and an increase in the organ weight, incidence and severity of histopathological changes (hepatocellular hypertrophy as well as reduced fatty turnover) in the liver. The liver as a main target organ is consistent with the findings in toxicokinetics, i.e. rapid and extensive absorption, metabolism and excretion of the test substance, and the liver retaining the highest radiolabel levels throughout the toxicokinetics studies (up to day 7 post dosing). The most sensitive species in repeat-dose toxicity studies was the rat, with the lowest no observed effect level (NOEL) in this species being 12.72/15.64 mg/kg bw/day (300 ppm), established in the 2-year chronic toxicity and carcinogenicity study.

In addition to the liver, the thyroid was another target organ identified in rats, but not in mice or dogs. Similar to the liver changes, a treatment dose-dependent and temporally related increase in thyroid weight and the incidence of histopathological changes (follicular hypertrophy and/or hyperplasia) were detected in long term repeat dose studies in rats (in particular the 2-year combined chronic and carcinogenicity study and the two-generation reproduction study).

Mutagenicity

Salmonella typhimurium exposed to up to the limit dose of 5000 µg/plate of the substance was not mutagenic in the bacterial reverse mutation assay with and without S9 metabolic activation.

Genotoxicity

Fenpyrazamine was not genotoxic in several *in vitro* and *in vivo* studies.

Carcinogenicity

There was no evidence of carcinogenic potential in a 78-week carcinogenicity study in mice by dietary administration up to and including the highest dose tested of 349/551 mg/kg bw/day (4000 ppm) for males/females, respectively.

In a 2-year carcinogenicity study in rats, increased neoplasia incidence only occurred at the highest dose tested of 2400 ppm (106.76/130.25 mg/kg bw/d for male/female), and consisted of hepatocellular carcinoma (4%), thyroid follicular carcinoma (6%), testes Leydig cell tumour (8%) and skin/subcutis keratoacanthoma (14%) in males; and uterine adenocarcinoma (4%) in females. While thyroid follicular carcinoma was at the upper historical control limit, and Leydig cell tumour, skin/subcutis keratoacanthoma and uterine adenocarcinoma were within historical control values,

hepatocellular carcinoma was above concurrent and historical controls. In discussing this finding, the applicant has indicated that:

> *"The incidence of hepatocellular carcinoma in high dose [2400 ppm] males (4%) was only slightly higher than the maximum historic control rate of 2.8% in male rats. In the absence of any increase in altered foci or pre-neoplastic lesions in the livers of treated male rats it is difficult to conclude that the slight increase in the incidence of hepatocellular carcinoma above that of historical control rates represents a true carcinogenic effect";* and
>
> *"The lack of an increase observed for precursor events in the genesis of hepatocellular carcinoma, such as foci of cellular alternation and neoplastic nodules in treated animals, does not support a role for fenpyrazamine in tumour induction".*

The OCS notes that the marginal increase identified occurred at the high dose (2400 ppm) only, without incidence/frequency at lower doses, and that hepatocellular adenoma frequency was identical to concurrent controls. Additionally, pre-neoplastic lesions (e.g. hyperplasia) were not noted in the histopathology, and no changes in the period to onset were identified (noting that hepatocellular carcinoma was only identified at terminal sacrifice, and animals presenting with hepatocellular carcinoma survived to final termination). On available data (noting mechanistic data and/or a mode of action (MOA) framework consideration of the observed effects were not provided), the OCS considers that on weight of evidence the test material is unlikely to have induced the hepatocellular carcinomas observed in the 2-year rat study, and that fenpyrazamine is unlikely to be carcinogenic.

Reproduction and developmental toxicity

In the two-generation reproduction study in rats, fenpyrazamine caused an increased incidence of post implantation loss, postnatal loss and lower pup weight for F_1 and F_2 pups/litters at ≥1000 ppm (72.5 mg/kg bw/d), doses where parental toxicity in P and F_1 adult animals was observed (increased organ weight and histopathological changes occurred in the liver and thyroid).

Developmental studies in rats revealed various visceral and skeletal variations including abnormal lobation and supernumerary lobe in the liver, left sided umbilical artery, skull zygomatic arch fusion, and costal cartilages asymmetrically aligned at sternum >125 mg/kg bw/d. Maternal toxicity at 125 mg/kg bw/d was present as only a slightly (but occasionally statistically significantly) lower accumulated body weight gain. Comparable NOELs were seen in the reproduction study (20.3 mg/kg bw/d minimum) and the developmental study (30 mg/kg bw/d) in rats.

In rabbits, implantation loss and abortion/premature delivery was a finding consistently observed in the dose range finding study and the formal study at ≥50 mg/kg bw/d, with a dose-dependent pattern. However, overall, fenpyrazamine did not cause external, visceral and skeletal malformations or variations of toxicological significance in the presented studies, and it is considered that fenpyrazamine is not a reproductive or a developmental toxicant.

Observations in humans

No information was provided.

Public exposure

The product is not intended to be applied by domestic users.

Application of the product by airblast may lead to unintended bystander exposure *via* chemical spray drift. This may be in the form of a single random exposure or repeat exposures of residents who reside adjacent to areas being treated with the product. Parameters for assessing bystander exposure have not been finalised by the APVMA.

The most likely route of public exposure to these products is through consumption of residues in food. Assessment of the exposure of the Australian population to residues of agricultural and veterinary chemicals in food crops and target animals is performed by the Australian Pesticides and Veterinary Medicines Authority (APVMA), with the support of, and using procedures and databases provided by, Food Standards Australia New Zealand (FSANZ).

International regulations

No information was provided. The Scheduling Secretariat has found the following:

In February 2013, the US Environmental Protection Agency (EPA) granted unconditional registration of fenpyrazamine. The uses for the substance are almond, small fruit vine climbing subgroup, head and leaf lettuce, low growing berry subgroup, blueberry subgroup, cranberry subgroup, ginseng, pistachio and ornamentals.

In July 2012, the European Union (EU) approved the use of fenpyrazamine with an effective date for this decision of 1 January 2013.

Scheduling status

Fenpyrazamine is not specifically scheduled.

Scheduling history

Fenpyrazamine has not been previously considered for scheduling; therefore, scheduling history is not available.

Fenpyrazamine belongs to the pyrazole chemical group. Pyrazole substances, such as penflufen and sedaxane, are listed in Schedule 5.

In October 2012, the delegate, based on the Advisory Committee on Chemicals Scheduling (ACCS) advice, decided to list penflufen in Schedule 5.

In May 2012, the delegate made a delegate only decision to list sedaxane in Schedule 5 based on its low toxicity profile.

Fenpyrazamine presents its fungicidal activity through inhibition of germ tube elongation and mycelium elongation. A similar fungicidal mode of acting chemical namely fenhexamid was listed in Appendix B (for agricultural uses) in 1999.

Pre-meeting public submissions

No submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that preparations containing more than 40 per cent of fenpyrazamine be listed in Schedule 5 as a new entry.

The committee supported the implementation date of 1 June 2015.

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:

- Overall toxicity profile of the substance is consistent with listing in Schedule 5.

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*;
- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that a new entry in Schedule 5 be created for fenpyrazamine, with a cut-off to exempt at 40 per cent. The low acute and chronic toxicity of fenpyrazamine and its overall toxicity profile is consistent with the Scheduling Policy Framework criteria for listing in Schedule 5. While there were some findings of carcinogenic potential in the long-term rat study, the lack of any supportive precursor events leading to carcinoma formation, in addition to there being no findings of carcinogenicity in a mouse study, tend to discount the significance of human carcinogenic potential as a matter for scheduling consideration. The delegate agrees with the ACCS that listing in Schedule 5 provides for warning levels and access controls more appropriate than if the chemical is listed in Appendix B. Furthermore, an appropriate set of First Aid and Safety Directions are recommended to the APVMA to be applied to the exempt product.

The delegate agrees with the implementation date 1 June 2015.

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

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.

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 5 – New entry

FENPYRAZAMINE except in preparations containing 40 per cent or less of fenpyrazamine.

1.7. Fluopyram

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the ACCS:

- To create a new Schedule 5 entry for fluopyram with appropriate low concentration cut-off to exempt from scheduling.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In August 2014, OCS, based on an application to the APVMA, requested that the delegate consider a proposal to include preparations containing 500 g/L or more of fluopyram in Schedule 5.

The reasons for the request were that the chemical:

- has low acute oral toxicity in female rats (LD_{50} >2000 mg/kg bw with no deaths or clinical signs of toxicity);
- has low acute dermal toxicity in male and female rats (LD_{50} >2000 mg/kg bw with no deaths or clinical signs of toxicity);
- has low acute inhalational toxicity in male and female rats (4-hr LC_{50} >5.1 mg/L the maximum obtainable concentration with no deaths);
- is not a skin irritant in rabbits;
- is not an eye irritant in rabbits; and
- is not a skin sensitiser in mice (LLNA).

The OCS evaluation report noted that the carcinogenic potential of the substance is of concern. Thyroid tumours were seen in male mice only and these were not considered relevant to humans. However, liver tumours were seen in female rats only, and while it is likely the mode of action (MOA) for these fluopyram induced liver tumours is similar to that developed for phenobarbital (which is not considered relevant to humans), there were data indicating AhR activation, which is not regarded as playing a role in phenobarbital's carcinogenic MOA. Therefore, further information is required on the association of fluopyram exposure and AhR activation and, in the absence of such data, the observed liver tumours could not be entirely discounted as being relevant to humans.

The assessment was originally undertaken as a Global Joint Review (GJR).

Germany considered the liver but not the thyroid tumours relevant for humans and classified fluopyram as a category 2 carcinogen (H351) according to the Globally Harmonised System for Classification and Labelling of Chemicals (GHS).

The US EPA considered the data insufficient to support the proposed carcinogenic MOA, resulting in possible irrelevance for humans of both tumour types. A prime deficiency was a lack of dose-response concordance with key precursor events and tumour incidence. Fluopyram was classified as "Likely to be Carcinogenic to Humans" based on tumours in two species and two sexes, and a linear low dose extrapolation model applied to animal data was recommended for quantitative estimation of human risk. Canada came to the same conclusion as the US EPA. US EPA based their risk estimate on the rat liver tumours but Canada on the mouse thyroid tumours (GJR).

At the national review stage, OCS concurred with Germany's interpretation of the tumour findings, and retained this position after the national evaluation. Like Germany, OCS considered fluopyram a category 2 carcinogen under the GHS (and a category 3 carcinogen under the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004)).

Delegate's reasons for referring this to the committee

The OCS scheduling recommendation is clear and has been supported by the applicant. However, the delegate decided to seek the advice of the ACCS, noting the discord between some of the regulatory agencies involved in the global evaluation of fluopyram in relation to the interpretation of the carcinogenic responses in male mice and female rats.

The Delegate asked the ACCS the following questions:

- Noting the different conclusions drawn by the US EPA, EU German rapporteur, Health Canada and JMPR in relation to the interpretation of the evidence relating to the Mode of Action (MoA) for the thyroid cancers seen in male mice and the hepatocellular adenomas seen in female rats at high doses, does the ACCS concur with the OCS assessment that the MoA evidence is sufficient to conclude that the tumours are of little or no relevance for human risk assessment, or have a clear threshold?
- Does the ACCS support the OCS recommendation that fluorpyram be listed in Schedule 5? Is the proposed Schedule 5 listing compatible with the OCS classification of fluopyram as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases: Xn; R40 Limited evidence of a carcinogenic effect?
- Does the ACCS agree that the product containing 50% fluopyram can be exempted from scheduling?

Substance summary

Fluopyram is a broad-spectrum fungicide with preventive, systemic and curative properties. It can be applied to plant foliage using ground, air-blast or aerial spray equipment. Fluopyram represents a new group of fungicide called pyridinyl ethylbenzimides that are succinate dehydrogenase inhibitors (SDHI) within the fungal mitochondrial chain, thus blocking electron transport[2].

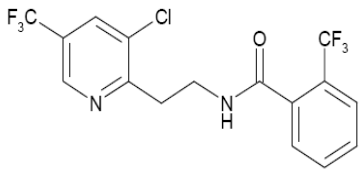

Figure 2. Structure of fluopyram

Acute toxicity

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

Toxicity	Species	Fluopyram	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2000	Low toxicity

[2] Fluopyram. New Active Ingredient Review April 2012, Minnesota Department of Agriculture. Accessed 26 August 2014. Available at http://www.mda.state.mn.us/chemicals/pesticides/regs/~/media/Files/chemicals/reviews/nair-fluopyram.ashx.

Toxicity	Species	Fluopyram	SPF classification
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	> 5112	Low toxicity
Skin irritation	Rabbit	Non-irritant	
Eye irritation	Rabbit	Non-irritant	
Skin sensitisation (local lymph node assay)	Mouse	Non-sensitiser	

The acute toxicity end-points for preparations containing 500 g/L of fluopyram are listed in the below table.

Toxicity	Species	Preparation containing 500 g/l of fluopyram	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	≥ 5000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	> 2091	Moderate to high toxicity
Skin irritation	Rabbit	Non-irritant	
Eye irritation	Rabbit	Non-irritant	
Skin sensitisation (local lymph node assay)	Mouse	Non-sensitiser	

Repeat-dose toxicity

In short-term and sub-chronic oral toxicity studies, the liver proved to be the main target organ in rats, mice and dogs. Hepatotoxicity became apparent by a dose-related increase in organ weight, alterations of clinical chemical parameters and histopathological findings such as centrilobular hypertrophy or periportal or midzonal vacuolation or macrovacuolation. In general, the adverse effects of fluopyram were more pronounced in rodents than in dogs. The lowest relevant no observed adverse effect level (NOAEL) was 12.5 mg/kg bw/d from the 90-day feeding study in rats, based on liver and kidney effects (organ weight increase, clinical chemistry and histopathological

findings (hyaline droplet nephropathy in the kidney)) at the next higher dose level of 60.5 mg/kg bw/d.

In chronic oral studies, the liver and kidneys remained the main target organs with an increase in organ weight that was sometimes accompanied by gross pathological findings; however, in mice, follicular cell hyperplasia in the thyroid gland was observed as well.

In a rat short-term dermal study, increased cholesterol, increased prothrombin time and increased liver weights associated with hepatocellular hypertrophy were seen at 1000 mg/kg bw/d. A NOAEL of 300 mg/kg bw/d was established based on these findings.

Genotoxicity and mutagenicity

Fluopyram was tested in a minimum battery of standard genotoxicity and mutagenicity tests *in vitro* and *in vivo*. These studies demonstrate that fluopyram has no genotoxic potential. There was no indication of gene mutation either in the presence or absence of metabolic activation in both the bacterial reverse mutation and mammalian gene mutation tests. The *in vitro* chromosome aberration test and the *in vivo* mouse micronucleus test were both negative and, thus, a clastogenic potential may be excluded.

Carcinogenicity

In a rat 2-year dietary study, the only treatment related carcinogenic finding was an increased incidence of combined hepatocellular adenoma and carcinoma in females at the top dose of 89 mg/kg bw/d (11/59 animals including 3 animals with carcinoma, compared to 2/60 in controls). No such finding was seen in males, noting that the top dose level of 750 ppm was reduced to 375 mg/kg bw/d from week 85 onwards due to the high mortality seen at 750 ppm, to give an overall study phase dose estimated to be 29 mg/kg bw/d.

In a mouse 18-month dietary study, the only treatment related carcinogenic finding was an increased incidence of follicular cell adenoma in males at the top dose level of 105 mg/kg bw/d (7/50 animals compared to 1/50 in controls). No such finding was seen in females at up to and including 129 mg/kg bw/d.

However, there was available evidence that rodents are much more susceptible to thyroid tumours than humans, and that the greater sensitivity of (particularly) male rodents to perturbations of the pituitary-thyroid axis by xenobiotics or physiologic alterations compared to humans is the result of:

- Higher circulating levels of TSH in rodents (>25 times) than humans;
- Shorter plasma half-life of T_4 in rodents (12-24 hours) than in humans (5-9 days); and
- Serum T_4 binding with high specificity to thyroxine-binding globulin (TBG) in humans which is absent in rodents. TBG has binding affinities 3-5 orders of magnitude greater than albumin or pre-albumin. This means the higher unbound T_4 is very susceptible to physiological events, like induced UDPGT, that enhance its clearance from blood.

Furthermore, by analogy with other agents (i.e. phenobarbital) known to induce thyroid tumours in rodents by CAR/PXR associated increases in Phase II enzymes metabolising free T_4 (as proposed for fluopyram), but not causing tumours in humans even after many years of therapeutic use, the MOA deduced for fluopyram rodent thyroid tumours is not considered relevant to humans.

Fluopyram was therefore considered as carcinogenic, as the observed liver tumours in female rats could not be entirely discounted as being relevant to humans.

Reproduction and developmental toxicity

There were no treatment related effects on reproductive performance in a dietary 2-generation rat study up to and including dose levels producing parental toxicity.

In a rat oral (gavage) developmental toxicity study, maternal bodyweight gain at 450 mg/kg bw/d remained static during gestation days (GD) 6-8 of treatment, resulting in an overall decrease in body weight gain of 16%. A similar but lower level effect was at 150 mg/kg bw/d with an overall body weight gain reduction of 6%. Food consumption at 450 mg/kg bw/d was decreased between 13 and 15% between GD 6 and 14. Developmental toxicity was observed at 450 mg/kg bw/d in terms of slightly lower fetal body weight (5%), and a slightly increased incidence of two visceral ('thymic remnant present' and 'ureter convoluted and/or dilated') and two skeletal minor variations ('at least one thoracic centrum split/split cartilage' and 'at least one thoracic centrum dumbbell and/or bipartite/normal cartilage'). The observed fetal findings at 450 mg/kg bw/d were considered a secondary non-specific of the observed marked maternal toxicity as shown by an overall decrease in body weight gain of 16%.

In a rabbit oral developmental toxicity study, at 75 mg/kg bw/d only very slight increases in maternal body weight gain were seen between GD 14-18 and GD 18-22, that resulted in an overall decrease in body weight gain of 35% between GD 6-29. These findings at 75 mg/kg bw/d were associated with decreases in food consumption between 24 and 34% for all intervals between GD 14-26. Developmental toxicity was observed at 75 mg/kg bw/d in terms of a 11% decrease in fetal body weight and a slight increase in the incidence of very small fetuses (classified as 'runts'). The observed fetal findings at 450 mg/kg bw/d were considered a secondary non-specific of the observed marked maternal toxicity as shown by an overall decrease in body weight gain of 35%.

Therefore, fluopyram was not considered a developmental toxicant in rats and rabbits.

Observation in humans

No information was provided.

Public exposure

Luna Privilege Fungicide is not intended for domestic use and therefore accidental exposure is not expected.

International regulations

No information was provided. The Scheduling Secretariat found the following information.

In February 2012, the US Environmental Protection Authority (EPA) registered the use of fluopyram on apples, banana, dry beans, cherries, peanuts, pistachios, potatoes, strawberries, sugar beets, tree nuts, watermelons and wine grapes to control a variety of diseases. Moreover, the degree of regulation by the US EPA indicates that fluopyram is classified as "Likely to be Carcinogenic to Humans".

The 2010 Joint FAO/WHO Meeting on Pesticide Residues (JMPR) indicated that the International Estimated Daily Intakes (IEDI) of fluopyram for the 13 Global Environment Monitoring System (GEMS)/Food regional diets, based on estimated supervised trial median residue (STMRs), were 1 to 6% of the maximum ADI of 0.01 mg/kg bw. The Meeting concluded that the long-term intake of residues of fluopyram from uses that have been considered by the JMPR is unlikely to present a public health concern. The International Estimated Short-term Intake (IESTI) varied from 0 to 4% of the ARfD (0.5 mg/kg bw) for the general population and 0 to 10% for children. The Meeting concluded that the short-term intake of residues of fluopyram from uses considered by the Meeting is unlikely to present a public health concern.

Scheduling status

Fluopyram is not specifically scheduled.

Fluopyram is a member of the chemical class namely pyridylethylamides. It is also identified as a member of the benzamide and pyridine class of fungicides.

Diflubenzuron (a benzmide class of substance) is listed in Schedule 5.

Pyridine fungicides, namely pyrifenox (Schedule 5), fluazinum (Schedule 6) and boscalid (Appendix B) are listed in the Poisons Standard.

Scheduling history

Fluopyram has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

No submissions were received.

Summary of ACCS advice to the delegate

The committee recommended an entry in Schedule 5 for preparations containing more than 50 per cent of fluopyram.

The committee supported the implementation date of 1 June 2015.

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:

- Evidence of a carcinogenic effect at high doses for which the mode of action has not been fully established.

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*;
- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that a new entry in Schedule 5 be created for fluopyram, with a cut-off to exempt at 50 per cent. The low acute and chronic toxicity of fluopyram, and its overall toxicity profile is consistent with the Scheduling Policy Framework criteria for listing in Schedule 5. The apparent differences in interpretation of the carcinogenicity findings between the three agencies that collaborated in the joint global review was noted. The purported mode of action (MoA) evidence at high levels of exposure tended to discount the significance of human

carcinogenic potential as a matter for scheduling consideration for at least the observed thyroid tumours. The proposed MoA for the hepatocellular tumours was not considered to be so conclusive. The delegate agrees with the ACCS that listing in Schedule 5 provides for appropriate warning levels and access controls. Furthermore, an appropriate set of First Aid and Safety Directions are recommended to the APVMA to be applied to the exempt product.

The delegate agrees with the implementation date 1 June 2015.

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

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.

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 5 – New entry

FLUOPYRAM **except** in preparations containing 50 per cent or less of fluopyram.

1.8. Methyl ethyl ketone oxime or 2-Butanone, oxime

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the ACCS:

- To amend the current Schedule 6 methyl ethyl ketone oxime entry to exempt from scheduling for silicone adhesive and sealant preparations containing 2.5% or less of methyl ethyl ketone oxime.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In May 2014, the delegate received an application to consider a proposal to amend the current Schedule 6 methyl ethyl ketone oxime (MEKO) entry to exempt from scheduling for silicone adhesive and sealant preparations containing 2.5% or less of MEKO.

The reasons for the request were:

- silicone adhesives and sealant preparations contain oximosilane cross-linkers and the corresponding hydrolysis product namely 2-butanone oxime (also known as MEKO).
- MEKO, in general, has irritation and skin sensitisation potential. Silicone adhesive and sealant preparations containing up to 7.1% of MEKO (in sum of free and hydrolysable MEKO), however, are not considered to be hazardous.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that, this matter was initially referred via a NICNAS IMAP report and considered at the November 2013 meeting of the

ACCS. At that time, the ACCS recommended listing in Schedule 6, with an exemption cut-off of 1%. A product sponsor has now requested reconsideration of the exemption cut-off for a specific range of products (silicone adhesives and sealants). The SPF suggests that the Delegate seek advice from the ACCS in relation to any re-scheduling application. The delegate noted that the application had been made using an appropriate format, and that supplementary toxicity studies had been provided in support of the submission.

The delegate sought the following specific advice from the ACCS:

- In accepting ACCS advice that methyl ethyl ketoxime be listed in Schedule 6, the delegate noted that the critical toxicological endpoints driving this categorisation (severe eye irritancy and sensitisation potential) are consistent with SPF factors for listing in Schedule 6, with the public health risk sufficiently ameliorated for products containing less than 1% to be exempted from scheduling.

- The delegate noted that the ACCS considered the sensitising potential of preparations similar to those the subject of this re-scheduling request. An extract from the records of the November ACCS 2013 meeting reflects this consideration:

"The Committee considered an appropriate low level cut-off to exempt from scheduling for methyl ethyl ketone oxime. It is anticipated that it would be used as an anti-skinning agent in the formulation of alkyd paints, varnishes, stains and coatings for domestic use and found at concentrations up to 1 per cent. The chemical will also be used as minor components in some silicone sealants (up to 5 per cent). It was noted that animals exposed to 3 per cent of methyl ethyl ketone oxime resulted in significant skin sensitisation. The Committee noted that preparations containing the substance would not be deliberately applied on to the skin therefore the risk at 1 per cent or less is tolerable rather than negligible. Members considered that a low concentration exemption cut-off at 1 per cent or less of methyl ethyl ketone oxime to exempt from scheduling would be appropriate."

- The skin sensitisation studies in the NICNAS IMAP report that lead to this conclusion were conducted with pure methyl ethyl ketoxime, at concentrations ranging from 3% to 50%.

- Noting that the applicant has submitted skin sensitisation studies that demonstrate no sensitisation potential for two products containing oximosilane cross-linked silicone, with some residual methyl ethyl ketoxime, does the ACCS support raising the exemption cut-off to 2.5% for this specific type of product?

- Does the ACCS support adoption of exemption clauses similar to those proposed in the application:

Schedule 6: METHYL ETHYL KETONE OXIME, except:

a. In viscous silicone adhesives or viscous silicone sealants containing 2.5 per cent or less of free methyl ethyl ketone oxime.

b. In other preparations containing 1 per cent of less of methyl ethyl ketone oxime.

Substance summary

MEKO is part of the chemical grouping discrete organics and the chemical sub-grouping oximes, or more specifically, ketoximes.

The most prevalent use of MEKO is as an anti-skinning agent in the formulation of alkyd paints[3], primers, varnishes and stains, to prevent oxidative drying and the formation of hard, gelatinous films on the surface of the paint product in the container. The majority of these uses were in the manufacture of alkyd paint products for both industrial and consumer applications. The substance is also present as a formulant in several pesticide products, namely wood preservatives and antifouling marine paints. In addition, it is a minor component of some sealants and adhesives and, to a lesser degree, of some fillers and artists' paint and printing materials.

MEKO is also used as a corrosion inhibitor in industrial boilers and water treatment systems and as a blocking agent in the manufacturing process of urethane polymers[4].

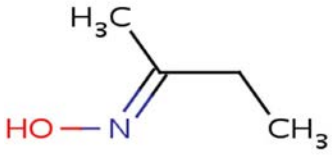

Figure 3. Structure of MEKO

Acute toxicity

The applicant provided skin irritation, eye irritation and skin sensitisation toxicity studies. In September 2013, NICNAS, under its IMAP programme, requested the delegate consider listing MEKO in Schedule 6. NICNAS provided an evaluation report and scheduling recommendation on MEKO.

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

Toxicity	Species	Methyl ethyl ketone oxime	SPF classification
Acute Oral LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute Dermal LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute Inhalational LC_{50} ($mg/m^3/4h$)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Slight irritant	
Skin sensitisation (Closed patch Test)	Guinea pig	Non-sensitiser	

[3] Burka, 1999 Methyl Ethyl Ketoxime (CAS No. 96-29-7) Administered in Drinking Water to F344/N Rats and B6C3F Mice. U.S. Department of Health and Human Services Public Health Service National Institutes of Health. Available at http://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox051.pdf.

[4] 2-Butanone, oxime (Butanone oxime) Environment Canada, Health Canada Available at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=32AD1FD8-1.

Repeat-dose toxicity

No information was provided.

Mutagenicity, genotoxicity and reproduction and developmental toxicity

No information was provided.

Observations in humans

No information was provided.

Public exposure

No information was provided.

The Secretariat obtained the following information from Health Canada's report on 2-butanone, oxime (butanone oxime)[5].

With regard to consumer products, butanone oxime is most prevalent in alkyd paints, stains, varnishes and coatings. Butanone oxime is also present in a few sealants, adhesives and fillers that are used mainly by industry, but which may also be available to the general population for home maintenance and do-it-yourself applications. Accordingly, use of alkyd paint containing butanone oxime was the primary scenario used to characterize exposure from products.

A limited number of studies report concentrations of butanone oxime during manufacture and use of products such as alkyd paints. A US study of consumer exposure to butanone oxime predicted a maximum concentration of butanone oxime in indoor air of 18 mg/m^3 based on the use of alkyd paint containing 0.293% w/w butanone oxime, the highest level of butanone oxime that was present in the products tested. A limited unpublished study measured butanone oxime concentrations of up to 9.9 ppm (30 mg/m^3) during a simulation using an indoor painting scenario with an alkyd paint containing approximately 0.2% butanone oxime.

There were no identified data on absorption of butanone oxime following inhalation exposure. While dermal absorption have been reported to range between 13% and 29% in a study conducted in rats, the estimates of internal exposure were derived using 100% uptake for inhalation and dermal absorption.

Based on the available information, the most likely route of exposure to butanone oxime for the general population is from inhalation during use of alkyd paints and coatings. However, in light of the limited data available on concentrations in environmental media, confidence in this estimate is very low.

International regulations

No information was provided.

The Secretariat has obtained the following.

No current use of butanone oxime in cosmetics has been notified in Canada[6].

[5] 2-Butanone, oxime (Butanone oxime). Health Canada. Available at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=32AD1FD8-1#a11.
[6] 2-Butanone, oxime (Butanone oxime) Environment Canada, Health Canada Available at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=32AD1FD8-1.

The use of butanone oxime in cosmetics is prohibited in Denmark and in the United Kingdom (in accordance with an amendment to Directive 76/768/EEC of the European Commission (European Commission 2004)[7].

The NICNAS's IMAP report notes the following restrictions apply:

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products; and
- New Zealand Cosmetic Products Group Standard. Schedule 4: Components Cosmetic Products Must Not Contain.

Scheduling status

Methyl ethyl ketone oxime is listed in Schedule 6 and Appendix E.

Schedule 6

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

Appendix E

Poisons	Standard statements
Methyl ethyl ketone oxime	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 - If in eyes washout immediately with water. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Other similar substances, such as methyl ethyl ketone and methyl ethyl ketone peroxide are included in Schedule 5 and Appendices E and F.

Schedule 5

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

Schedule 5

METHYL ETHYL KETONE PEROXIDE.

Scheduling history

In April 2014, the chemicals scheduling delegate, based on the advice from the ACCS, decided to include preparations containing more than 1% MEKO is Schedule 6. The delegate also decided to create an Appendix E entry for MEKO.

[7] Commission Directive 2004/93/EC of 21 September 2004. Available at http://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:32004L0093.

Pre-meeting public submissions

No submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that the current Schedule 6 methyl ethyl ketone oxime entry be amended to exempt from scheduling viscous silicone adhesives or viscous silicone sealants containing 2.5% or less of methyl ethyl ketone oxime.

The committee supported the implementation date of 1 June 2015.

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

The reasons for the recommendation comprised the following:

- The form of the presentation of this material mitigates the acute irritation and skin sensitisation effects at the relevant concentration.

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*;
- SPF Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate accepts the advice from the ACCS and agrees to add the proposed exemption clause to the current Schedule 6 entry for methyl ethyl ketone oxime. The additional information provided by a sponsor of silicone sealant products containing methyl ethyl ketone oxime shows that the risks or skin irritancy/sensitization are sufficiently ameliorated at concentrations up to 2.5%.

The delegate agrees with the implementation date 1 June 2015.

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; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

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.

The delegate has confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 6 – Amendment

METHYL ETHYL KETONE OXIME **except:**

a. in viscous silicone adhesives or viscous silicone sealants containing 2.5% or less of methyl ethyl ketone oxime; or

b. in other preparations containing 1 per cent or less of methyl ethyl ketone oxime.

2. Scheduling proposals referred to the November 2014 meeting of the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling (ACCS-ACMS #10)

2.1. SUMMARY OF FINAL DECISIONS

Substance	Final Decision
1-Butanol	**New Schedule 6 entry** n-BUTYL ALCOHOL **except** a. when included in Schedule 5; b. in preparations containing 5 per cent or less of n-butyl alcohol; or c. in preparations for cosmetic or therapeutic use other than in spray form. **New Schedule 5 entry** n-BUTYL ALCOHOL in preparations containing 10 per cent of less of n-butyl alcohol **except** a. for preparations containing 5 per cent or less of n-butyl alcohol; or b. in preparations for cosmetic or therapeutic use other than in spray form. **New Appendix E, Part 2 entry** n-BUTYL ALCOHOL – Standard statements A, E1, S1 **New Appendix F, Part 3 entry** n-BUTYL ALCOHOL – Warning statement 5, Safety directions

Substance	Final Decision
	2, 4, 8 Implementation date – 1 October 2015
1-Propanol	**New Schedule 6 entry** n-PROPYL ALCOHOL **except**; a. when included in Schedule 5; b. in preparations containing 5 per cent or less of n-propyl alcohol; or c. in preparations for cosmetic or therapeutic use other than in spray form. **New Schedule 5 entry** n-PROPYL ALCOHOL in preparations containing 10 per cent or less of n-propyl alcohol **except** a. for preparations containing 5 per cent or less of n-propyl alcohol; or b. in preparations for cosmetic or therapeutic use other than in spray form. **New Appendix E, Part 2 entry** n-PROPYL ALCOHOL – Standard statements A, E1 **New Appendix F, Part 3 entry** n-BUTYL ALCOHOL – Warning statement 5, Safety directions 1, 9 Implementation date – 1 October 2015
2-Cyclohexylphenol	**Amendment to Schedule 9 entry** CYCLOHEXYLPHENOLS **except**: a. when separately specified in these Schedules; or b. in preparations containing 0.5 per cent or less. Implementation date – 1 June 2015
Gamma butyrolactone	**New Appendix C/Schedule 10 entry** GAMMA BUTYROLACTONE (excluding its derivatives) in non-polymerised form in preparations for domestic and cosmetic use. Implementation date – 1 June 2015

Substance	Final Decision
Lemongrass oil	Pending
Oxalic acid (soluble oxalates)	**Amendment to Schedule 6 entry** OXALIC ACID **except:** a. in dental care preparations, including mouthwashes, containing 3% or less of soluble salts of oxalic acid; or b. its insoluble salts. Implementation date – 1 June 2015
Polihexanide	Pending

2.2. 1-Butanol

Scheduling proposal

The chemicals and medicines scheduling delegates (the delegates) referred the following scheduling proposal for consideration by the joint committee of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling (ACCS-ACMS):

- To create new schedules 5 and/or 6 entries with appropriate concentration cut-offs and associated warning statements.

The committee was asked to discuss and consider the proposal with an implementation date of 1 June 2015/1 October 2015 or 1 February 2016.

In August 2013, NICNAS, under the IMAP programme, requested that the chemicals delegate consider a proposal to include spray preparations containing 5% 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.

Delegates' reasons for referring this to the committee

The delegates 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.

1-butanol was first considered by the ACCS at the March 2014 meeting. The chemicals delegate felt, in view of the potential impact on existing products, that advice was needed from the ACCS, with an appropriate public notice alerting the industry to the proposed scheduling action. At this time, advice from the Therapeutic Goods Administration (TGA) suggested that 1-butanol was used as an excipient, which is why it was not originally referred to the joint ACCS-ACMS meeting in March. The inclusion of 1-butanol (as an excipient) in one AgVet product was considered by the ACCS.

The ACCS advised the delegate that preparations containing 1-butanol at concentrations greater than 10 per cent be placed in Schedule 6. Preparations containing between 5 and 10 cent 1-butanol should be placed in Schedule 5 and preparations containing 5 per cent or less of 1-butanol be

exempt from scheduling. Cosmetics and therapeutics were also to be exempted. The ACCS also recommended Appendix E Standard Statements of A, E1 and S1 and Appendix F Warning Statement 5 and Standard Statement 1, 4 and 8 (see Scheduling Status for these warnings/statements in full). The committee felt that the potential for moderate to severe eye damage or respiratory irritation consistent with the Scheduling Policy Framework (SPF) factors for Schedule 5 or Schedule 6 depending on concentration and use. The chemicals delegate supported the ACCS recommendation and published an interim decision based on the ACCS's recommendation. Based on advice received during consultation on the interim decision to include 1-butanol in Schedules 5 and 6, the chemicals delegate determined that the interim decision be set aside, and that further advice be sought on the specific range of products containing 1-butanol that would warrant scheduling to protect against eye damage. This information should form the basis as to whether these should include such products as aerosol or spray products and/or arts & craft materials, where there may be a greater risk of being taken into the eye. This may include further consideration by the joint ACCS-ACMS of the previous ACCS advice that 1-butanol in cosmetics and therapeutic goods be exempted from any proposed schedule entry.

The delegates asked the ACCS-ACMS the following questions:

- The principal issue raised by the NICNAS IMAP report is the potential for eye irritancy associated with concentrations of 1-butanol above 5%, with more serious eye damage expected at 10% 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-ACMS confirm the advice previously given by the ACCS 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 10%, and exempt below 5%?

- If scheduling is recommended, should this be limited to certain specific product types in the retail market e.g. only spray on products? 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)?

- Does the ACCS-ACMS confirm the Appendix E & F statements recommended by the ACCS for scheduled products captured by the proposed scheduling entries?

- 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; however, the scheduling proposal that was published in the initial interim decision on 27 June 2014 has been attached below.

Schedule 6 – New entry

1-BUTANOL **except**

a. when included in Schedule 5;

b. in preparations containing 5 per cent or less of 1-butanol; or

c. in preparations for cosmetic or therapeutic use.

Schedule 5 – New entry

1-BUTANOL in preparations containing 10 per cent of less of 1-butanol **except**

a. for preparations containing 5 per cent or less of 1-butanol; or

b. in preparations for cosmetic or therapeutic use.

Appendix E, part 2 – New entry

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

Appendix F, part 3 – New entry

Poison	Warning statement	Standard direction
1-butanol	5. Irritant.	1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

Scheduling history

1-Butanol has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

Four submissions were received.

One submission believes scheduling of 1-butanol is unnecessary. However, if controls were deemed necessary, products containing up to 10% should be exempt from scheduling and any scheduling controls should be restricted to products in aerosol or spray formats.

One submission supports the exclusion of therapeutic goods from any proposed schedule entry.

One submission noted that 1-butanol is used in very low concentrations in a number of therapeutic and cosmetic products with no issues they were aware of. The submission recommends any scheduling decision should ensure that current cosmetic and therapeutic products for which no safety issues have been identified are not affected.

One submission highlighted the concern is in aerosol product applications where ocular exposure can lead to irreversible eye damage, which could be controlled through appropriate scheduling of aerosol use of the chemical.

Summary of ACCS-ACMS advice to the delegates

The committee recommended that preparations containing 1-butanol at concentrations greater than 10 per cent in Schedule 6 except when in Schedule 5 except for preparations containing 5 per cent or less of 1-butanol. 1-Butanol used in cosmetic and therapeutic preparations except for those in spray form is to be exempted from scheduling. The committee also recommended appropriate Appendix E and F statements (provided below) for 1-butanol.

The committee discussed an extended implementation to allow industry to manage stock in hand, due to the impact on domestic cleaning products containing between 5-10%.

The committee supported an implementation date of 1 October 2015.

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:

- Acute and ocular toxicity of the substance.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Delegates' interim decision

The delegates accept the advice of the ACCS-ACMS to include 1-butanol in Schedules 5 and 6, under the listing name n-butyl alcohol, with an index cross-reference to the name 1-butanol. 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 delegates also accept the ACCS-ACMS recommendation that cosmetics and therapeutic products, other than spray products, be specifically exempted. The recommendation to include spray products in the proposed Schedule 6 and 5 listings is because they represent a greater risk of accidental eye damage. The delegates noted an industry submission that suggested eye damage with spray products would be of minimal risk because they are designed to be sprayed away from the body. The delegates rejected this as a basis for extending the cosmetic/therapeutic use exemption to all such products.

The delegates agree with the implementation date being 1 October 2015.

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.

Public submissions on the interim decision

One public submission was received, which supported the Delegates' interim decision.

Delegates' final decision

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

The delegates have confirmed the proposed implementation date of 1 October 2015.

Schedule entry

Schedule 6 – New entry

n-BUTYL ALCOHOL **except**

a. when included in Schedule 5;

b. in preparations containing 5 per cent or less of n-butyl alcohol; or

c. in preparations for cosmetic or therapeutic use other than in spray form.

Schedule 5 – New entry

n-BUTYL ALCOHOL in preparations containing 10 per cent of less of n-butyl alcohol **except**

a. for preparations containing 5 per cent or less of n-butyl alcohol; or

b. in preparations for cosmetic or therapeutic use other than in spray form.

Appendix E, Part 2 – New entry

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

Appendix F, Part 3 – New Entry

Poison	Warning statements	Safety direction
n-butyl alcohol	5. Irritant.	1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

2.3. 1-Propanol

Scheduling proposal

The delegates referred the following scheduling proposal for consideration by the joint committee of the ACCS-ACMS:

- To create new schedules 5 and/or 6 entries with appropriate concentration cut-offs and associated warning statements.

The committee was asked to discuss and consider the proposal with an implementation date of 1 June 205/1 October 2015 or 1 February 2016.

In August 2013, NICNAS, under the IMAP programme, requested that the chemicals 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 these substances may be required.

Delegates' reasons for referring this to the committee

The delegates considered the proposal 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 concentration cut-offs to Schedule 5 and to exempt from scheduling.

The matter was first considered by the ACCS at the March 2014 meeting. The chemicals delegate felt, in view of the potential impact on existing products, that advice was needed from the ACCS, with an appropriate public notice alerting the industry to the proposed scheduling action. At the

time, advice from the APVMA and TGA suggested that 1-propanol is not used in products they regulate; which is why the matter was not referred to the joint ACCS-ACMS meeting in March.

The ACCS advised the delegate that preparations containing 1-propanol at concentrations greater than 10 per cent be included in Schedule 6. Preparations containing between 5 and 10 per cent 1-propanol be included in Schedule 5 with preparations containing 5 per cent or less of the substance be exempt from scheduling. Cosmetics and therapeutics were also to be exempted. The ACCS also recommended Appendix E Standard Statements of A and E1 and Appendix F Warning Statement 5 and Standard Statement 1 and 9 (see Scheduling Status for these warnings/statements in full). The committee felt that the potential for moderate to severe eye damage was consistent with the SPF factors for Schedule 5 or Schedule 6 depending on concentration and use.

Based on advice received during consultation on the interim decision from the March 2014 ACCS meeting to include 1-propanol in Schedules 5 and 6, the chemicals delegate determined that the interim decision be set aside and further advice be sought on the specific range of products containing 1-propanol that would warrant scheduling to protect against eye damage. This information would be useful in determining whether the schedule entries 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 or spray products where there may be a greater risk of being taken into the eye. This may include further consideration by the joint ACCS/ACMS meeting of the pervious ACCS advice that 1-propanol in cosmetics and therapeutic goods be exempted from any proposed schedule entry.

The delegates asked the ACCS-ACMS 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%, with more serious eye damage expected at 10% 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, art, 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-ACMS confirm the advice previously given by the ACCS 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 10%, and exempt below 5%?

- If scheduling is recommended, should this be limited to certain specific product types in the retail market e.g. on spray-on products? 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)?

- Does the ACCS/ACMS confirm the Appendix E & F statements recommended by the ACCS for scheduled products captured by the proposed schedule entries?

- 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 publicly 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; however, the scheduling proposal that was published in the initial interim decision on 27 June 2014 has been included below.

Schedule 6 – New entry

1-PROPANOL **except**:

a. when included in Schedule 5;

b. in preparations containing 5 per cent or less of 1-propanol; or

c. in preparations for cosmetic or therapeutic use.

Schedule 5 – New entry

1-PROPANOL in preparations containing 10 per cent or less of 1-propanol **except**:

a. for preparations containing 5 per cent or less of 1-propanol; or

b. in preparations for cosmetic or therapeutic use.

Appendix E, part 2 – New entry

Poison	Standard statement
1-propanol	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

Poison	Warning statement	Standard direction
1-propanol	5. Irritant.	1. Avoid contact with eyes. 9. Use only in well ventilated area.

Scheduling history

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

Pre-meeting public submissions

Four submissions were received.

One submission believes scheduling of 1-propanol is unnecessary. However, if controls were deemed necessary, these controls should be restricted to the aerosol or spray format products containing >10% 1-propanol.

One submission supports the exclusion of therapeutic goods from any proposed schedule entry.

One submission noted that 1-propanol is used in very low concentrations in a number of therapeutic and cosmetic products with no issues they were aware of. The submission recommends any scheduling decision should ensure that current cosmetic and therapeutic products for which no safety issues have been identified are not affected.

One submission highlighted the concern is in aerosol product applications where ocular exposure can lead to irreversible eye damage, which could be controlled through appropriate scheduling of aerosol use of the chemical.

Summary of ACCS-ACMS advice to the delegates

The committee recommended that preparations containing more than 10 per cent 1-propanol be included in Schedule 6 except when in Schedule 5, except for preparations containing 5 per cent or less of 1-propanol. 1-Propanol used in cosmetic and therapeutic preparations, other than for those in spray form, are to be exempted from scheduling. The committee also recommended appropriate Appendix E and F statements (provided below) for 1-propanol.

The committee discussed an extended implementation to allow industry to manage stock in hand, due to the impact on domestic cleaning products containing between 5-10%.

The committee supported the implementation date of 1 October 2015.

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:

- Acute and ocular toxicity of the substance.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Delegates' interim decision

The delegates accept the advice of the ACCS-ACMS to include 1-propanol in Schedules 5 and 6, under the listing name n-propyl alcohol, with an index cross-reference to the name 1-propanol. 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 delegates also accept the ACCS-ACMS recommendation that cosmetics and therapeutic products, other than spray products, be specifically exempted. The recommendation to include spray products in the proposed Schedule 6 and 5 listings is because they represent a greater risk of accidental eye damage. The delegates noted an industry submission that suggested eye damage with spray products would be of minimal risk because they are designed to be sprayed away from the body. The delegates rejected this as a basis for extending the cosmetic/therapeutic use exemption to all such products.

The delegates agree with the implementation date being 1 October 2015.

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.

Public submissions on the interim decision

One public submission was received, which supported the Delegates' interim decision.

Delegates' final decision

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

The delegates have confirmed the proposed implementation date of 1 October 2015.

Schedule entry

Schedule 6 – New entry

n-PROPYL ALCOHOL **except**;

a. when included in Schedule 5;

b. in preparations containing 5 per cent or less of n-propyl alcohol; or

c. in preparations for cosmetic or therapeutic use other than in spray form.

Schedule 5 – New entry

n-PROPYL ALCOHOL in preparations containing 10 per cent or less of n-propyl alcohol **except**:

a. for preparations containing 5 per cent or less of n-propyl alcohol; or

b. in preparations for cosmetic or therapeutic use other than in spray form.

Appendix E, Part 2 – New entry

Poison	Standard statements
n-propyl alcohol	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

Poison	Warning statements	Safety direction
n-propyl alcohol	5. Irritant.	1. Avoid contact with eyes. 9. Use only in well ventilated area.

2.4. 2-Cyclohexylphenol

Scheduling proposal

The delegates referred the following scheduling proposal for consideration by the joint committee of the ACCS-ACMS:

- to create a new Schedule 6 entry for 2-cyclohexylphenol with appropriate exemption cut-offs for some specific uses, and to amend, as necessary, the current entry in Schedule 9 for CYCLOHEXYLPHENOLS.

The delegates asked that the joint committee of ACCS-ACMS consider the following:

- revise the preamble to Appendix A to confirm that the listed exemptions do not apply to Schedule 9, and/or
- revise the current schedule 9 generic entry for cyclohexylphenols or develop a separate and specific Schedule 6 entry for 2-cyclohexylphenol, so that the current Schedule 9 entry can remain, and/or
- review the current listing of industrial algicides, bacteriocides and slimicides in Appendix A to see whether this exemption should be maintained.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

The delegates' proposal was based on an inquiry from a company regarding paint preparations containing 2-cyclohexylphenol as a bacteriocide. The substance is not specifically scheduled. An Appendix A listing for bacteriocides for industrial use that do not fit the definition of an agriculture or veterinary chemical product may be applicable for this substance.
The chemicals delegate considered the inquiry, and noted that in February and June 2006, the National Drugs and Poisons Schedule Committee (NDPSC) considered industrial biocides. At that time, there was a complex discussion on the need to schedule 'industrial biocides'. There had been some earlier (and later) actions that included four biocides in Schedule 6, based on their acute toxicity and skin corrosivity. The delegate indicated that it was recognised that these scheduling actions contradicted an earlier policy (1993 Drugs and Poisons Scheduling Committee) that biocides for 'industrial use' did not require scheduling unless there was a clear indication that they could be used in domestic products. The four biocides, which are listed in Schedule 6 (N-coco-1,3-diaminopropane; N-oleyl-1,3-diaminopropane; alkoxylated fatty alkylamine polymer; and N-tallow alkyl-1,3-propanediamine diacetate/tallow alkylamine acetates) , are assumed to be listed because they are possibly used in domestic products.

At the February 2006 meeting, the NDPSC originated the Appendix A blanket exemption of industrial algicides, bacteriocides and slimicides from scheduling. There were discussions at both the February and June 2006 meetings regarding whether an industrial biocide is too broad a term, and whether it includes, or not, all such compounds that require registration by the APVMA. The

NDPSC decided if they are registered by the APVMA, scheduling actions could apply, but if they are not, the Appendix A exemption should apply. The Appendix A clause was modified at the June 2006 NDPSC meeting to ensure that the Appendix A exemption only applied to biocides not requiring registration by the APVMA.

If the biocide 2-cyclohexylphenol is assessed by NICNAS, and not the APVMA, it would seem to fit within the Appendix A exemption.

The information from the company was that 2-cyclohexylphenol will be used as an 'industrial biocide' in paints; therefore, the Appendix A exemption would probably apply.

The chemicals scheduling delegate indicated that cyclohexylphenols are currently listed in Schedule 9 except when separately specified in these schedules. The reason for this listing is not explicit. The reason for this listing could be that these chemicals may be used as an analogue or precursor in the synthesis of psychoactive compounds.

Delegates' reasons for referring this to the committee

The delegates' reason for referring this scheduling proposal to the joint meeting of the ACMS-ACCS is that, there is some confusion about whether the proposed use of this chemical in an industrial biocide satisfies the current Appendix A exemption for such products and whether any Appendix A exemption applies to chemicals listed in Schedule 9. Accordingly, the delegates seek advice from the joint committee of the ACCS-ACMS.

The delegates asked the ACCS-ACMS the following questions:

- Does the proposed use of 2-cyclohexylphenol in paints as a bacteriocide qualify for the general scheduling exemption for such use in Appendix A?
- Is it clear that 2-cyclohexylphenol's function in paints is for its bacteriocidal properties, or is it simply an impurity?
- The preamble to Appendix A states that "*this Standard does not apply to a poison in any of the following products*". Does this statement need amending to indicate that the exemption does not apply to poisons listed in Schedule 9? Some States have indicated that they do not adopt Appendix A, or would not apply it in the case of Schedule 9 poisons.
- Irrespective of whether Appendix A applies to this use, is it necessary to develop a new specific entry in Schedule 6 for 2-cyclohexylphenol? Would this then totally exempt this specific isomer from Schedule 9, because of the current entry wording (CYCLOHEXYLPHENOLS **except** when separately specified in these schedules) or should any new S6 entry specify the use covered by the entry?
- Would a low-level cut-off for an S6 entry cause an exempted product to revert to S9, or would the current wording of the S9 entry allow for exempt products associated with a specified use?
- Are there any implications for loss of control over illicit drug manufacture if the above changes are made?

Substance summary

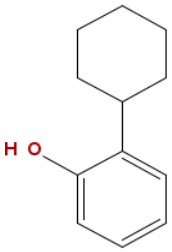

Figure 4. Structure of 2-cyclohexylphenol

Acute toxicity

Toxicity	Species	2-cyclohexylphenol	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	4100	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits	5010	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not available	Not available	Unable to assess
Skin irritation	Rabbit	Corrosive	
Eye irritation	Rabbits	Severe eye irritant	
Skin sensitisation (add here the type of test if it is stated in the report)	Not available	Not available	

International regulations

2-cyclohexyphenol is listed in the European Inventory of Existing Commercial Chemical Substances (EINECS).

Scheduling status

2-Cyclohexylphenol is not specifically listed in a schedule.

Cyclohexylphenol is listed in Schedule 9.

Schedule 9

Cyclohexylphenol **except** when separately specified in these Schedules.

Algicides, bacteriocides and slimicides for industrial use are listed in Appendix A.

Appendix A

ALGICIDES, BACTERIOCIDES OR SLIMICIDES for industrial use that do not fit the definition of an agvet chemical product.

Scheduling history

2-Cyclohexylphenol has not been considered previously.

In August 1973, the Drugs and Poisons Schedule Committee (DPSC) considered a request for advice as to whether industrial biocides would require poisons scheduling and, if so, what toxicological data would be required. The DPSC indicated that such industrial products did not require scheduling and should be assessed by the Chemicals Safety Unit/Worksafe as part of the registration process and to be labelled in the context of their end use. However, where the product was to be available for use in the home, it would need to be referred to DPSC for scheduling (and labelling).

In February 2006, the National Drugs and Poisons Schedule Committee (NDPSC) originated the Appendix A blanket exemption of industrial algicides, bacteriocides and slimicides from scheduling. There was discussion at both the February and June 2006 meetings regarding whether 'industrial biocide' is too broad a term, and whether or not it includes all such compounds that require registration by the Australian Pesticides and Veterinary Medicines Authority (APVMA). The NDPSC decided that if they are registered by the APVMA, scheduling actions could apply, but if they are not, the Appendix A exemption should apply. The Appendix A clause was modified at the June 2006 NDPSC meeting to ensure that the Appendix A exemption only applied to biocides not requiring registration by the APVMA.

Pre-meeting public submissions

One submission was received that supports exemption of certain product categories from Schedule 9 and requested certain uses of 1-cyclohexylphenol should instead be included in Schedule 6, with exemption from scheduling if contained in a formulated product.

Summary of ACCS-ACMS advice to the delegates

The committee recommended that the current scheduling of 2-cyclohexylphenol remains appropriate. The committee recommended Appendix A exemption should not apply to substances in Schedule 9.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Delegates' interim decision

The Delegates accept the advice of the Joint ACCS-ACMS meeting, that the current Schedule 9 entry for cyclohexylphenol remains appropriate and that this entry would cover the proposed use of 2-cyclohexylphenol in paints. The Delegates note that, while the use of 2 -cyclohexylphenol as a biocide in paints could qualify for exemption under the Appendix A general exemption for *ALGICIDES, BACTERIOCIDES OR SLIMICIDES for industrial use that do not fit the definition of*

an agvet product, there remains some potential confusion about whether an entry in Schedule 9 overrides such an exemption. The Delegates therefore propose to consult with State/Territory jurisdictions on whether the preamble to Appendix A or a specific amendment to Part 1 of the SUSMP is needed to clarify that an entry in Schedule 9 overrides an Appendix A exemption.

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

Public submissions on the interim decision

One public submission was received. The submission noted that a biocide (*ortho*-phenylphenol) with cyclohexylphenol impurity is currently used in industrial setting, and that they have concerns that clarifying an entry in Schedule 9 overrides an Appendix A exemption could potentially have a significant impact. The submission requests the Delegates reconsider the interim decision and propose an alternate Schedule 9 entry be considered:

CYCLOHEXYLPHENOLS **except**:

a. when separately specified in these Schedules; or

b. in preparations containing 0.5 per cent or less.

Delegates' final decision

The delegates note the submissions received in response to publication of the interim decision and have determined to vary the interim decision by amending the current Schedule 9 entry for CYCLOHEXYPHENOLS, to allow a scheduling exemption for products containing a low concentration. The delegates were persuaded that the presence of 2-cyclohexylphenol as an inadvertent manufacturing byproduct in the biocide o-phenylphenol would not enable extraction of cyclohexylphenol for illicit purposes. However, advice from the jurisdictions that the current listing of cyclohexylphenol in Schedule 9 at any concentration would negate the product exemption for industrial biocides available under Appendix A would result in a significant regulatory impact on products containing 2-cyclohexylphenol as an impurity.

The delegates have therefore determined to amend the Schedule 9 entry in accordance with the proposal in the public submission.

Schedule 9 - vary the entry to:

CYCLOHEXYLPHENOLS **except**:

a. when separately specified in these Schedules; or

b. in preparations containing 0.5 per cent or less.

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

The delegates agree to a proposed implementation date of 1 June 2015.

Schedule entry

Schedule 9 – Amendment

CYCLOHEXYLPHENOLS **except**:

a. when separately specified in these Schedules; or

b. in preparations containing 0.5 per cent or less.

2.5. Gamma butyrolactone

Scheduling proposal

The delegates referred the following scheduling proposal for consideration by the joint committee of ACCS-ACMS:

- To consider whether a separate entry for gamma butyrolactone is required in either Appendix C/Schedule 10 or Schedule 9 to restrict its use in cosmetics or other types of products.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/1 October 2015/1 February 2016.

In June 2014, the Drug Control Section (DCS), now with the TGA, asked the delegates to consider the scheduling of gamma butyrolactone, suggesting a potential entry in Appendix C for cosmetic use.

DCS regulates the import, export, and manufacture of controlled drugs and chemicals to fulfil Australia's obligations under international drug conventions and national legislation received a number of enquiries regarding the importation. The section received a number of inquiries regarding the importation of acetone free nail wipes which contain gamma butyrolactone as it is a known chemical precursor for the manufacture of the Schedule 9 substance gamma-hydroxybutyric acid (GHB). A summary of the reasons why the scheduling request was lodged by DCS has been provided below:

- Gamma-butyrolactone (GBL) is a substance which is known to metabolised, when ingested, into gamma-hydroxybutyric acid (GHB and a Schedule 9 substance) and can be also used as a chemical precursor to manufacture GHB.

- GBL is currently available for retail sale in Australia and is being imported as a component of acetone free nail wipes (15-17mL in a container of 30 nail wipes).

- A search of the internet identified incidences where persons were using similar acetone-free nail wipes at night clubs and at least one report of an infant going into a coma.

- Of concern is the metabolism of GBL to GHB. This is similar to the incidence with bindeez beads some years ago where children were exposed to 1,4 butanediol when the beads were ingested. Bindeez beads were recalled by the ACCC and an Appendix C entry was made in the Poisons Standard.

- Noting that GBL is also legitimately used by industry for various industrial purposes, we are seeking options under the scheduling framework to help determine whether the use of GBL in a cosmetic does/does not pose a risk to public health. If a risk is identified options could include an Appendix C entry restricting its use in consumer (cosmetic) products.

Delegates' reasons for referring this to the committee

The delegates' reason for referring this scheduling proposal to the ACMS-ACCS was that this matter requires advice from committees because the possible scheduling actions include consideration of a current Schedule 9 listing for gamma hydoxybutyrate (GHB) and a possible Appendix C listing for gamma butyrolactone (GBL), with a potentially large overlap in the types of products affected by any scheduling decision.

The delegates asked the ACCS-ACMS the following questions:

- Is the potential for extensive conversion of GBL to GHB by metabolism sufficient reason to consider restrictive scheduling for all/any products formulated with GBL?
- Do the provisions of SUSMP Part 1 (2) imply that GBL should be considered a 'derivative', 'active principle' or stereoisomer of GBH, and thus be already captured by the Schedule 9 entry for GBH or the Appendix C entry for 1,4-butanediol?
- If scheduling action is required to restrict the use of GBL in commercial products, should this be via Schedule 9 or Appendix C, and should the scheduling be limited to specific products types (e.g. cosmetics, nail wipes)?
- What weight should be given to media and published reports outlining abuse patterns or inadvertent toxicity of acetone-free nail wipes overseas? Should information be sought on whether this type of abuse or toxicity has been reported in Australia?
- What could be the unintended consequences of any proposed scheduling action on products already on the market where GBL has been used as a solvent or minor ingredient?

Evaluation

The delegates determined that an external evaluation was not required for this scheduling proposal.

Substance summary

Drug monographs to not appear to be available for gamma butyrolactone; however, the following links have been provided for general background:

- European Chemicals Agency: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9e95c3-5f03-3da6-e044-00144f67d249/AGGR-b7c3efb3-0a19-4402-a3b9-261e20b05a7c_DISS-9d9e95c3-5f03-3da6-e044-00144f67d249.html#section_1.1
- Gamma-butyrolactone (GBL) Critical Review Report, World Health Organisation Expert Committee on Drug Dependence paper, Thirty-sixth Meeting June 2014: http://www.who.int/medicines/areas/quality_safety/4_3_Review.pdf?ua=1

As listed in the WHO paper, GBL has wide spread industrial use. It is an intermediate in the synthesis of polyvinylpyrrolidone, DL-methionine, piperidine, phenylbutyric acid and thiobutyric acid. It is used as a solvent for polyacrylonitrile, cellulose acetate, methylacrylate polymers, and polystyrene. It is a constituent of paint removers, textile aids and drilling oils.

International regulations

European Union: GBL is a non-scheduled drug precursor and in accordance with the EU legislation on control and monitoring of trade in drug precursors (Regulation (EC) No 273/2004(4) and Regulation (EC) No. 111/2005(5)), GBL is covered by the EU voluntary monitoring scheme for drug precursors.

Australia: GBL is a border controlled substance and is illegal to import into Australia without a permit. The importation of a commercial quantity of a border controlled drug (over 1 kg of GBL) is punishable by up to life imprisonment and/or an $825,000 fine.

Austria: GHB was included in the list of substances controlled by the Austrian Narcotic Substances Act in 2003. In November 2008 amendments to the Decree on Narcotic Drugs were sent out for examination. They include the synthetic substances BZP and GBL as well as the opiate Oripavin.

Bulgaria: From April 2010 both GHB precursors (GBL and 1,4-BD) are enlisted in Schedule III - "Dangerous substances".

Canada: GBL is a Controlled Substance under Schedule VI of the "Controlled Drugs and Substances Act" in Canada. Schedule VI of the "Controlled Drugs and Substances Act" requires vendors to collect information regarding purchases of GBL. The Act also prohibits the import and export of GBL into or out of Canada classifying it as either an indictable offense punishable with up to 10 years in prison or an offense punishable on summary conviction liable to imprisonment for up to eighteen months. It is not illegal for an individual to possess GBL in Canada.

Germany: GBL is not listed in the narcotics law, but its distribution is controlled. Possession is not illegal, but may be punished according to the Medicines Act, when intended to be sold for human consumption or synthesis of GHB. In recent years, an increase of GBL consumption has been observed due to the prohibition of GHB.

Hong Kong SAR: GBL is a dangerous drug controlled under Schedule 1 of the Dangerous Drugs Ordinance, Cap.134 (with exemption clause at Paragraph 16D). Any person who is found to have in his possession of it not in accordance with this Ordinance can be liable, on conviction upon indictment, a fine of HK$1,000,000 and to imprisonment for 7 years.

Israel: GBL has been classified as a proscribed substance since 2007.

The Netherlands: September 2011, based on the CAM advice, the Minister of Health has recently decided to promote GHB from class 2 to class 2 of the Opium law. It is now in the class of hard drugs. It is advocated to place GBL and 1,4 BD in the highest class of the Wvmc (European trade treaty; 273/2004).

Poland: GBL is not classified as a drug and can be purchased in chemistry shops as a solvent.

Romania: GBL is controlled by Governmental decision that entered in force on 15 February 2010.

Sweden: February 1st, 2000 GHB was scheduled in Sweden. Since 1 September 2005 GBL and 1,4-butandiole are also under control.

United Kingdom: GBL has been classified as a Class C drug since 23 December 2009, with a prison term of up to two years for possession and 14 years for dealing.

Norway: 1,4-butandiol and GBL were added to the Norwegian National Drug List with effect from 24 March 2010.

Scheduling status

Gamma butyrolactone is not currently scheduled. It is, however, a precursor for the Schedule 9 substance 4-hydroxybutanoic acid (gamma hydroxybutrate or GHB).

Scheduling history

In November 1996, the NDPSC decided to include gamma butyrolactone in Schedule 9. This decision was rescinded in June 2002.

Pre-meeting public submissions

One submission was received that states any scheduling consideration should be restricted to gamma butyrolactone and not include its derivatives. The submission also notes that scheduling controls should be limited to the types of products that could be misused, i.e. where gamma butyrolactone is a major ingredient in the product with no other toxic or unpleasant tasting ingredients, or where gamma butyrolactone can be easily extracted from the product.

Summary of ACCS-ACMS advice to the delegates

The committee recommended gamma butyrolactone be included in Appendix C (soon to be Schedule 10), exempting the polymerised form, in preparations for domestic and cosmetic use.

The committee supported the implementation date of 1 June 2015.

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

The reasons for the recommendation comprised the following:

- It has industrial uses, for which controls are in place through other mechanisms.
- GBL is a is a well-known drug precursor that can be used for illicit manufacture of GHB, is also metabolised to GHB *in vivo* and, therefore, has no place in domestic or cosmetic products.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Delegates' interim decision

The Delegates accept the advice of the Joint ACCS-ACMS meeting, to create a new entry in Appendix C/Schedule 10 to restrict the use of gamma butyrolactone (GBL) in cosmetic and domestic preparations. These restrictions are necessary to prevent potential diversion of this well-known drug precursor to illicit use or in manufacture of GHB, a substance controlled in Schedule 9. An industry submission suggested that the EU permits use of GBL as a solvent in some cosmetics and, while GBL use in Australian products may be quite low, it should not represent an abuse problem because it is difficult to extract from products like nail polishes and hardeners. However, the delegates were also informed of some instances where such products had been abused. Accordingly, the interim decision is to restrict its use *via* listing in Appendix C/Schedule 10.

The delegates agree with the implementation date being 1 June 2015.

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

Public submissions on the interim decision

One public submission was received, which supported the Delegates' interim decision.

Delegates' final decision

The delegates note the submissions received in response to publication of the interim decision and confirm the interim decision as no evidence has been received to alter the interim decision. The

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

The delegates have confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Appendix C/Schedule 10 – New entry

GAMMA BUTYROLACTONE (excluding its derivatives) in non-polymerised form in preparations for domestic and cosmetic use.

2.6. Oxalic acid (soluble oxalates)

Scheduling proposal

The delegates referred the following scheduling proposal for consideration by the joint committee of the ACCS-ACMS:

- At the March 2014 meeting of the ACCS, an issue was raised regarding whether soluble oxalate salts used in therapeutic goods such as mouthwashes would be captured by the current Schedule 6 entry *OXALIC ACID **except** its derivatives and insoluble salts*. This issue needs to be clarified along with the need for a specific clause exempting soluble oxalates in mouthwashes.

The committee was asked to discuss and consider the resolutions with an implementation date of 1 June 2015/ 1 October 2015/1 February 2016.

Delegates' reasons for referring this to the committee

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

The delegates asked the ACCS-ACMS the following question:

- ACCS consideration of a proposal to review the current Schedule 6 entry for oxalic acid raised an issue of whether mouthwashes containing soluble oxalates would be captured by the current wording, which specifies that the entry exempts derivatives of oxalic acid and its insoluble salts. Can soluble oxalates used in mouthwashes be considered to be 'derivatives', or is there a need to create a separate exemption for this specific use?

Scheduling history

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

In August 2014, the delegate considered a scheduling application requesting that the Schedule 6 entry for oxalic acid be amended to either exempt from scheduling household and domestic cleaning preparations containing 8% or less oxalic acid, or to list such products in Schedule 5. The delegate made a final decision, based on advice received from the ACCS and the public submissions received, not to change the scheduling status of oxalic acid. The delegate indicated that the toxicity profile of oxalic acid is consistent with the SPF Schedule 6 criteria and 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 noted that the available information was insufficient to develop an exemption threshold for the Schedule 6 entry at that time. The delegate noted 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 delegate concluded that the matter of providing an exemption threshold for the use of soluble oxalates in mouthwashes requires further consideration and it would be referred back to a future meeting of the ACCS-ACMS.

Public pre-meeting submissions

Five submissions were received. All supported the exclusion of oral care preparations (e.g. mouthwashes, but also other products such as swabs) containing soluble oxalates from scheduling. Most submissions agreed that the cut-off concentration for exempting these products should be <3%. However, one submission requested an exemption for therapeutic oral care products which provide <20 mg oxalic acid per day. One submission also requested exempting household and domestic cleaning products containing <8% oxalic acid. Three submissions supported appropriate labelling for consumers, but that this should align with the statements already in use in the European Union.

Summary of ACCS-ACMS advice to the delegates

The committee recommended that current Schedule 6 oxalic acid schedule entry be amended to exempt for mouthwash preparations containing potassium oxalates at less than 1.5% from scheduling, and remove the exemption of derivatives.

The committee supported the implementation date of 1 June 2015.

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:

- low toxicity of potassium salts, at low concentrations, in mouth wash products.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Delegates' interim decision

The delegates accept the advice of the ACCS-ACMS to exempt mouthwashes containing soluble salts of oxalic acid from the current Schedule 6 entry for OXALIC ACID. However, the Delegates also note advice included in pre-meeting submissions that soluble oxalates in mouthwashes and therapeutic dental preparations may contain up to 3% soluble oxalates. Accordingly, the delegates vary the proposed Schedule 6 amendment to incorporate the 3% exemption.

The delegates agree with the implementation date being 1 June 2015.

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

Public submissions on the interim decision

Three public submissions were received. All supported the Delegates' interim decision.

Delegates' final decision

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

The delegates have confirmed the proposed implementation date of 1 June 2015.

Schedule entry

Schedule 6 - Amendment

OXALIC ACID **except:**

a. in dental care preparations, including mouthwashes, containing 3% or less of soluble salts of oxalic acid; or

b. its insoluble salts.

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

3. Agricultural and veterinary chemicals

3.1. Metaflumizone

Scheduling proposal

In January 2015, the OCS, based on an application made to the APVMA to register a new active constituent (and a new production source for the active constituent) for agricultural uses, requested that the delegate consider confirming the existing entry for metaflumizone in Schedule 5 of the SUSMP.

The reasons for the request are discussed below.

A toxicological data package was submitted by the applicant to support the approval of a new active constituent, metaflumizone (for agricultural use), and to seek registration of a new product which contains 0.063% metaflumizone. The product is used for the control of nuisance ant species on gardens, golf courses, lawns, parks, turf and sports grounds, and industrial areas (including home garden use).

The OCS notes that this is the first consideration of metaflumizone for agricultural use. Previous applications to the OCS and referral of the chemical to the NDPSC for consideration in 2007 have been for veterinary uses of metaflumizone. The current application provides supplementary

toxicology information on metaflumizone, which were considered and relied on in the evaluation report and recommendations to the APVMA.

Substance summary

Metaflumizone is a new semicarbazone insecticide. It works by binding selectively to the slow-inactivated state of a sodium channel, hence blocking sodium channels in target insects, and resulting paralysation and damaged nerve activity. It is proposed to be used in products for treating gardens, golf courses, industrial areas, lawns etc.

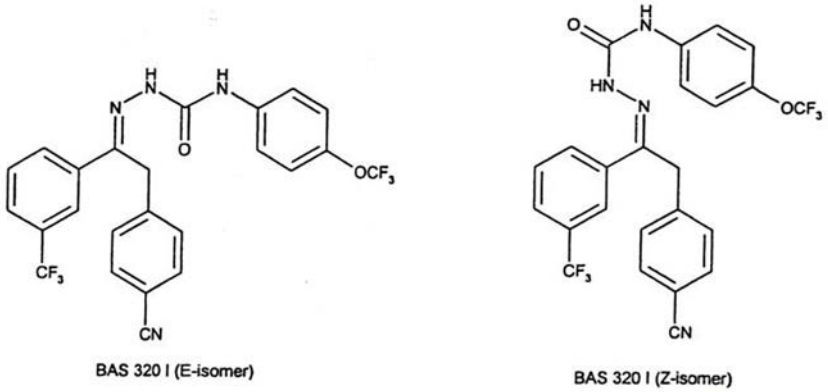

Figure 5. Structure of metaflumizone (E- and Z-isomers)

Acute toxicity

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

Toxicity	Species	Metaflumizone	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 5000 (no deaths)	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 5000 (one death, not substance-related)	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	> 5200 (head/nose exposure)	N/A
Skin irritation	Rabbit	Non irritant	N/A
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (M&K method)	Guinea Pig	Non-sensitiser	N/A

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

Toxicity	Species	Metaflumizone	SPF classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (F only, no deaths)	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (M&F, no deaths)	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	N/A
Skin irritation	Rabbit	Slight irritant	Schedule 5
Eye irritation	Rabbit	Non irritant	N/A
Skin sensitisation (Standard LLNA)	Guinea Pig	Sensitiser (up to 25% positive response on challenge)	Schedule 6[#]

[#] *While a dermal sensitiser would be considered consistent with Schedule 6 listing according to the SPF, the OCS emphasises that a GLP-compliant dermal sensitisation study was conducted on the active constituent, which reported no sensitisation response. This suggests that the sensitisation observed in the study with the product formulation is likely attributable to product excipients rather than the active constituent.*

Toxicokinetics/ADME

Overall, oral absorption of metaflumizone was low, with ~23% oral bioavailability when taken up in feed admixtures and ~11% when administered by oral gavage. Recovery of administered material was high, with the majority of the material eliminated in faeces and minimal urinary excretion.

There was strong evidence of metaflumizone accumulation in tissues, particularly in the fat. After 14 days of daily dosing at 30 mg/kg bw, the metaflumizone concentration was up to 43 times higher in the fat than that detected following a single dose (26 times higher in muscle and plasma, 13 times higher in liver and kidney) (Afzal & Zulalian, 2002). The uptake of lipophilic compounds from blood into fat is essentially a passive process and a compound like metaflumizone with a high Log K_{ow} will readily partition into the fat of animals. The rate of entry and exit into fat are governed by both the lipophilicity and the effective concentration gradient between blood and fat (Fick's laws of diffusion). A high plasma to fat tissue ratio of ~1:250 for metaflumizone was apparent after 14 days of repeated dosing in rats.

Repeat-dose toxicity

Toxicity in rats and dogs was characterised by general non-specific signs of toxicity including reduced food consumption, reduced bodyweight gain, poor general state, ataxia, salivation and lateral position after repeated dosing. Mice were considered to be the least sensitive species for metaflumizone and did not exhibit any of these signs of toxicity up to a dose of 1000 mg/kg bw/d inclusive during a lifetime study. The lowest dose for metaflumizone's effects was 30 mg/kg bw/d in dogs (the LOEL in a 3-month and 1-year oral study). General signs of toxicity were also observed in a 2-generation rat reproduction study at a maternotoxic LOEL of 50 mg/kg bw/d, in a

rat developmental study at a maternotoxic LOEL of 120 mg/kg bw/d and in a 3-month rat neurotoxicity study at a LOEL of 150 mg/kg bw/d.

Mutagenicity/genotoxicity

Metaflumizone or its impurities/metabolites were not genotoxic.

Carcinogenicity

Metaflumizone was not carcinogenic.

Reproduction and developmental toxicity

Metaflumizone was not a reproductive or developmental toxicant at the doses tested in the various studies.

Other toxicology endpoints

On the basis of this evidence, metaflumizone is not considered likely to be a neurotoxicant in humans. No evidence of developmental neurotoxicity was noted in the range-finding DNT study.

Metaflumizone was not immunotoxic by the sRBC or the splenic NK cell assays.

Observation in humans

No information was provided.

Public exposure

The product is proposed to be used in gardens, golf courses, industrial areas, lawns, parks, turf and sports grounds. The product may be used by domestic users, as well as professional users.

While exposure modelling as part of the OCS evaluation concluded that the systemic risks were acceptable and margins of exposure were not considered unsafe, the OCS noted that Section 3.6.5 of the current APVMA Data Guidelines (*Guideline for pesticides intended for domestic use*) indicates that: *"Domestic pesticide products should present a low risk from repeated use. For instance, such products should be unlikely to induce irreversible toxicity."* The OCS considers that the dermal sensitisation potential of the product does **not** match the *'low risk from repeated use'* criteria, noting that there is no specific PPE prescribed for dermal sensitisers, and has recommended a restriction to 'professional use only' for the product.

The Applicant has indicated in their initial comments on the report that new risk reduction technologies are being developed and that a subsequent application for use of the product in domestic situations will be assembled in the future. This is not expected to have any specific bearing on the scheduling proposal (noting OCS' comments above regarding the lack of dermal sensitisation potential for the active constituent metaflumizone).

International regulations

No specific information is available.

Scheduling status

Metaflumizone is currently listed in Schedules 5.

Schedule 5

METAFLUMIZONE.

Scheduling history

Metaflumizone was first time considered by the National Drugs and Poisons Scheduling Committee (NDPSC) in October 2007. The committee noted the following from the draft report:

- On the basis of its overall low toxicity profile and its accumulative and persistent nature, the approval of metaflumizone is supported subject to the following conditions:
  - the active metaflumizone is only for use in non-food producing animals or on non-food producing plants; and
  - the active metaflumizone is only suitable for those use patterns where there is no human exposure to the product containing metaflumizone or to its residues; and
  - any application for a product containing the active metaflumizone and proposing a new use pattern would require an occupational health and safety assessment for each new product application and use pattern.
- Whilst noting that the acute toxicity of metaflumizone was low, on the basis of the slight eye irritation in rabbits and its tendency to accumulate in body fat, the NDPSC may wish to consider placing it in Schedule 5.

The Committee noted that the metaflumizone toxicological database was complete and all of the submitted studies were well conducted and performed in accordance with contemporary test guidelines. All submitted studies were considered adequate and were relied upon to enable the recommendations to be made.

The Committee generally agreed that the toxicity of metaflumizone was very low, with only slight eye irritation being of any note. However, Members noted that metaflumizone was very lipid soluble and could bioaccumulate.

The Committee generally agreed the low toxicity together with the bioaccumulation potential, constituted a risk that could be adequately addressed through a Schedule 5 listing and the product registration process.

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- OCS evaluation report (not publicly available);
- Section 52E of the *Therapeutic Goods Act 1989*;
- SPF scheduling factors;
- Other relevant information.

Delegate's final decision

The toxicology profile of metaflumizone is consistent with SPF criteria for listing in Schedule 5, and consistent with the 2007 decision of the NDPSC to list it in Schedule 5. No new information is contained in the current submission that would cause that decision to be changed. This position is supported in both the OCS evaluation report and by the product sponsor. Accordingly, the delegate confirms that listing of metaflumizone in Schedule 5 remains appropriate, with no exemption cut-off. The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods*

Act 1989 include (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) toxicity.