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

April 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 initially referred to the **November 2014** meeting of the Advisory Committee on Chemicals Scheduling (ACCS#12);
- scheduling proposals initially referred to the **November 2014** joint meeting of the ACCS and the Advisory Committee on Medicines Scheduling (ACMS) (joint ACCS-ACMS#10).

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 http://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 an interim decision on an application, the delegate may make a final decision either confirming, varying or setting aside

the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead 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 as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the Poisons Standard on ComLaw, is available at http://www.tga.gov.au/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
CAS	Chemical Abstract Service
CIR	Cosmetic Ingredient Review
CPS	Committee on Poisons Schedules
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

Table of contents

Part A - Final 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)

SUMMARY OF DELEGATE'S FINAL DECISIONS

Substance	Final Decision
1,4-benzenediamine, 2-nitro-	**Schedule 6 – Amendment** † PHENYLENEDIAMINES including alkylated, arylated and nitro derivatives not elsewhere specified in these Schedules: a) in preparations packed and labelled for photographic purposes; b) in preparations packed and labelled for testing water **except** tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool"; c) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. written in letters not less than 1.5 mm in height; or d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement: WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height.

Substance	Final Decision
	Appendix C – Amendment PHENYLENEDIAMINES, including alkylated, arylated and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows **except** when included in Schedule 6. **Appendix E, Part 2 – Amendment** Phenylenediamines including alkylated, arylated and nitro derivatives • in hair dyes. Warning statements A, E1 Phenylenediamines including alkylated, arylated and nitro derivatives • in preparations other than hair dyes. Warning statements A, G1, G3, E1, S1 Implementation date - 1 June 2015
Formaldehyde donor	**Part 1, Interpretation** "Free formaldehyde" includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol and formaldehyde released from formaldehyde donors. Implementation date - 1 February 2016
Methylated spirit(s)	**Schedule 5 – New Entry** METHYLATED SPIRIT(S) when packed and labelled as a 'biofuel' suitable for use in 'spirit burners'. **Appendix F, Part 1 - New Statement** METHYLATED SPIRIT(S) - warning statement 107 **Appendix F, Part 3 - New Entry** Methylated spirit(s) when packed and labelled as a 'biofuel' suitable for use in 'spirit burners' - warning statement 107 Implementation date - 1 February 2016

1.1 1,4-Benzenediamine, 2-nitro

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 a new Schedule entry for 1,4-benzenediamine, 2-nitro- in Schedule 6 and Appendix C of the SUSMP or to modify the existing Schedule 6 and Appendix C entries for PHENYLENEDIAMINES to ensure that it captures this 2-nitro derivative.

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

In August 2014, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under the Inventory Multi-tiered Assessment Prioritisation (IMAP) programme, requested that the delegate consider a proposal to create a new entry for 1,4-benzenediamine, 2-nitro- in Schedule 6 and Appendix C that copies the entries for 'Phenylenediamines'.

The NICNAS assessment report noted that although there is a group entry for 'Phenylenediamines and alkylated phenylenediamines' in Schedule 6 and Appendix C, this group entry does not include nitro substituted derivatives of phenylenediamines.

NICNAS recommended that the entries in Schedule 6 and Appendix C of the SUSMP for 'Phenylenediamines' be applied to this nitro-substituted derivative of a phenylenediamine.

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 programme had referred another phenylenediamine for scheduling consideration. This one is a 2-nitro derivative, referred with the chemical name 1,4-benzenediamine, 2-nitro-. There are existing generic SUSMP entries for phenylenediamines *and their alkyl derivatives not elsewhere specified in the schedules* in Schedule 6 and Appendices C, E and F. The Schedule 6 entry exempts preparations for dyeing hair and eyelash/eyebrow when labelled with warning statements for skin irritation and eye damage, while the Appendix C entry precludes use in preparations for skin colouration and dyeing eyelash/eyebrow (except when in Schedule 6). The delegate considered that the advice of the ACCS is needed on whether to develop separate entries for this compound in Schedule 6 and Appendices C, E and F, or to amend the existing generic entry.

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the NICNAS IMAP report has raised issues that require amendment to the existing entries for PHENYLENEDIAMINES in Schedule 6, or Appendices C, E and F? Specifically, does the ACCS support the proposed broadening of the generic entries to include the 2-nitro derivative, or is a separate listing the preferred option?

- Is the *in vitro* (but not *in vivo*) mutagenicity potential for the 2-nitro derivative sufficient reason to prevent use in all hair dye and eyelash/eyebrow dyeing preparations, by creating a separate entry in Appendix C banning these uses?

- Given that the 2-nitro derivative appears to share the sensitising potential of other phenylenediamines, are additional warning statements needed to specifically address this toxicological endpoint if the chemical is separately listed in the Schedules?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for 1,4-benzenediamine, 2-nitro-. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1093

Scheduling status

1,4-Benzenediamine, 2-nitro- is not specifically scheduled.

As the substance belongs to phenylenediamine chemical group, the schedule listing for phenylenediamine is provided below.

Schedule 6

† PHENYLENEDIAMINES [including ~~and]~~ alkylated [and arylated] phenylenediamines not elsewhere specified in these Schedules: [changes in parentheses come into effect on 1 July 2015]

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

c) in hair dye preparations except when the immediate container and primary pack are labelled with the following statements:

   KEEP OUT OF REACH OF CHILDREN, and

   WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

   written in letters not less than 1.5 mm in height; or

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

   WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

   written in letters not less than 1.5 mm in height.

Appendix C

PHENYLENEDIAMINES, including alkylated and arylated derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

Appendix E

Poisons	Standard statements
Phenylenediamines including both alkylated and arylated phenylenediamines	
• in hair dyes.	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 - If in eyes wash out immediately with water.
• in other preparations.	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). G1 - Urgent hospital treatment is likely to be needed. (Note – the words 'at once' to be added to instruction A). G3 - If swallowed, do NOT induce vomiting. E1 - If in eyes wash out immediately with water. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Appendix F

Poisons	Warning statements	Safety direction
Phenylenediamines including both alkylated and arylated phenylenediamines		
• in hair dyes.	21. WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dying eyelashes or eye brows; to do so may be injurious to the eye.	
• in preparations other than hair dyes.		1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

Scheduling history

1,4-Benzenediamine, 2-nitro- is not specifically scheduled.

As 1,4-benzenediamine, 2-nitro- belongs to the phenylenediamines chemical group, the scheduling history for phenylenediamines is provided below.

In January 1955, the Committee on Poisons Schedule decided to list phenylene toluene and other alkylated benzene diamines in Schedule 2. At that time Schedule 2 substances were considered to be poisons, the sale of which was restricted to certain specified categories of vendors and which were subject to identical packing and labelling requirements to those of Schedule 1 but which were not required to be entered in a Poisons Register.

In March 1980, the Poisons Schedule Committee (PSC) decided to delete the Schedule 6 aromatic amines entry and amend the Schedule 6 phenylenediamines entry to include alkylated phenylenediamines.

In May 1985, the PSC noted that a number of phenylenediamines in Schedule 6 were individually listed as well as being included in the general entry for phenylenediamines. The PSC agreed that the individual entries were not required in addition to the general entry for phenylenediamines and decided to delete the individual entries. The PSC agreed that no change was required to the Schedule 2 phenylenediamines entry.

In August 2000, the National Drugs and Poisons Schedule Committee (NDPSC) agreed to exempt hair dye products containing phenylenediamines or toluenediamines from scheduling, conditional upon specified labelling.

In February and June 2004, the NDPSC considered the outcomes of investigations into incorrectly packed and labelled eyelash/brow tints containing phenylenediamines/toluenediamine and in October 2004, the NDPSC agreed to foreshadow amendments to prohibit use for eyelash/brow tinting. This proposal was varied by the February 2005 NDPSC meeting which instead agreed to foreshadow two options: to allow either salon use only, or all domestic use, of these eyelash/brow tints as Schedule 6 products (when compliant with the specified labelling).

In June 2005, the NDPSC concluded that the potential risk of causing a strong allergic response in a small number of individuals could be minimised through appropriate labelling. The NDPSC therefore agreed to that eyelash/brow tints were Schedule 6 poisons when appropriately labelled.

In June 2006, the NDPSC considered a request for flexibility in applying the mandatory labelling for eyelash/brow tints containing phenylenediamine and toluenediamine. The NDPSC indicated that, as the main risk was sensitisation, which in this case did not demonstrate a clear dose response, strong label warnings were required before such products could be available as Schedule 6. As there was a risk of separation of an outer pack from the immediate container, it was appropriate that all mandatory labelling continued to be applied to the immediate container, regardless of pack size. That the Schedule 6 warning statement would need to be applied, whether the use was domestic or industrial, or the product would default to Appendix C. The NDPSC further confirmed that the introduction to both Appendix E and F provided sufficient flexibility to allow for variation of product use and formulation.

In February 2007, the NDPSC considered the labelling requirements for single use composite pack hair preparations, including those containing phenylenediamines or toluenediamine, in view of amending various references to ‘hair dyes’ to ‘hair preparations’. The NDPSC decided not to amend these references as there was potential for inadvertent capture of products for non-dying use patterns.

In February 2008, the NDPSC considered the scheduling of phenylenediamine and toluenediamine in eyelash/brow tints including restrict non-professional supply to ≤5 mL and limit non-professional supply to ‘complete kit’ forms (i.e. all reagents). The NDPSC agreed that it was not appropriate to address separate supply of a developer for eyelash/brow tinting through the scheduling process as there was little evidence of an actual public health risk from products not being sold in ‘complete kit’ form. The NDPSC also agreed that there was little evidence to support a pack size restriction on the availability of eyelash/brow tints containing phenylenediamine/toluenediamine.

In April 2014, the delegate considered three phenylenediamine dyes and referred them to the ACCS for advice. In July 2014, the ACCS considered the delegate’s proposal to amend the phenylenediamine group entry and recommended that the Schedule 6 phenylenediamine group entry be amended to include arylated derivatives. The ACCS also recommended that a new Appendix C entry be created for skin colouration (including tattooing), hair dye, eyelash and eyebrow tinting preparations containing 1,2-benzenediamine and 1,3- benzenediamine.

Pre-meeting public submissions

One submission was received that tentatively supports the inclusion of 1,4-benzenediamine, 2-nitro- in hair dyes in Appendix C.

Summary of ACCS advice to the delegate

The committee recommended that the current Schedule 6 and Appendix C entries for phenylenediamines be amended to explicitly include nitro derivatives.

The committee recommended appropriate Appendix E and F statements for phenylenediamines.

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:

- Similar toxicity profile to other scheduled phenylenediamines.

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 scheduling of the phenylenediamines is complex and it has been considered over a number of years. It uses a combination of listing in Appendix C, to restrict their use in certain types of dye products where the risks of mutagenicity and skin/eye irritancy are unacceptable (skin colouration and dyeing of eyebrows and eyelashes), and listing in Schedule 6 for hair dyes and other permitted products where label warning statements can provide appropriate protection to product users. In July 2014, the ACCS recommended some changes to the scheduling of phenylenediamines to further restrict the use of those considered to have the highest mutagenic potential and to ensure that the generic Schedule 6 entry included both alkyl and aryl derivatives. The current proposal seeks to expand the generic Schedule 6 phenylenediamine entry to include nitro derivatives, on the basis that they share a common toxicological profile and there uses, particularly in hair dyes, require similar restrictive scheduling.

The delegate notes the industry submission that tentatively supports inclusion in Appendix C of the use of 1,4-benzenediamine, 2-nitro- in cosmetics, on the basis that such uses are banned in the European Union. However, the delegate notes advice from the ACCS that evidence for the mutagenic potential of 1,4-benzenediamine, 2-nitro- is not as strong as with the 1,2- and 1,3-benzenediamines added to Appendix C to prevent use in cosmetics. Therefore, the restrictions in the current Schedule 6and Appendix C generic entries for phenylenediamines are considered as appropriate for the nitro derivative, as they are for the alkyl and aryl derivatives.

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; (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

† PHENYLENEDIAMINES including alkylated, arylated and nitro derivatives not elsewhere specified in these Schedules:

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water **except** tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

c) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN, and
>
> WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

> WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix C – Amendment

PHENYLENEDIAMINES, including alkylated, arylated and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

Appendix E, Part 2 – Amendment

Poison	**Standard Statement**
Phenylenediamines including alkylated, arylated and nitro derivatives	
• in hair dyes.	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 - If in eyes wash out immediately with water.
• in preparations other than hair dyes.	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). G1 -Urgent hospital treatment is likely to be needed. (Note – the words 'at once' to be added to instruction A). G3 - If swallowed, do NOT induce vomiting. E1 - If in eyes wash out immediately with water. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Appendix F, Part 3 – Amendment

Poison	Warning Statement	Standard Statement
Phenylenediamines including alkylated, arylated and nitro derivatives		
• in hair dyes.	21. WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dying eyelashes or eye brows; to do so may be injurious to the eye.	
• in preparations other than hair dyes.	28. (Over) (Repeated) exposure may cause sensitisation.	1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

1.2 Formaldehyde donors

Scheduling proposal

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

- To include the specified seven formaldehyde donor chemicals in the index of the SUSMP with a cross-reference to the formaldehyde schedule entries or to develop separate entries in Schedules 2 and 6, and Appendix C, that mirror the formaldehyde entries in those Schedules.

The committee was asked to discuss and consider the resolutions with an implementation date of either 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:

- An amendment to the current listing of formaldehyde in the SUSMP be considered to include the specified formaldehyde donor chemicals in the index to the SUSMP with a cross reference to formaldehyde.

Formaldehyde in cosmetic products is controlled under the SUSMP, and these controls apply to formaldehyde present in cosmetics for any reason. Therefore, the chemicals proposed are already subject to controls; however, the clarity of this link should be improved.

The reasons for the request were:

- Skin sensitisation is a concern for cosmetic products containing these chemicals as preservatives,
- Quaternium 15 (CAS No. 4080-31-3 and CAS No. 51229-78-8) is also a teratogen.

Delegate's reasons for referring this to the committee

The delegate's reason for referring this scheduling proposal to the ACCS was that, this is a complex scheduling matter where the delegate required advice from the ACCS. The key issue was whether the seven chemicals listed in the NICNAS IMAP report should be separately listed in the same Schedules as formaldehyde, with the same exemptions, or whether cross-referencing to formaldehyde via the SUSMP index is sufficient.

The Delegate asked the ACCS the following questions:

- The scheduling history of formaldehyde is quite complex. The latest considerations were in May 2012, when the delegate, acting on advice from the February 2012 ACCS meeting, agreed to proposals to clarify the meaning of the definition 'free formaldehyde' in Part 1 of the SUSMP. This clarification included cross-referencing methylene glycol in the SUSMP index as the hydrated form of formaldehyde in aqueous solution.
- Would cross-referencing the seven IMAP- listed compounds to formaldehyde in the SUSMP index achieve a similar outcome to the cross-referencing of methylene glycol?
- Would cross-referencing in the SUSMP index imply that all the scheduling restriction relevant to the formaldehyde entries in Schedules 2, 6 and Appendix C (including the exemptions) would apply to products containing any of the seven compounds at the relevant concentrations? Put another way, would jurisdictional poisons regulations adopt relevant restrictions if the chemicals are only listed in the SUSMP index?
- Given that the listed compounds all have different molecular weights, would the concentration cut-offs currently in the formaldehyde entries be appropriate for each 'formaldehyde donor'?
- Would it be clearer if the seven compounds were separately listed in Schedules 2 and 6, with the same (or different) concentration cut-offs and exemptions as formaldehyde?
- Would it be necessary to create parallel entries for all seven formaldehyde donors in Appendix C?
- The NICNAS IMAP report contains only limited information on the toxicological properties for most of the chemicals outside the sensitisation and systemic toxicity of the released formaldehyde, although there is a suggestion that one of them (Quaternium 15) is suspected to have teratogenic potential. Is the limited available toxicological data sufficient to inform individual scheduling decisions?
- Is there an alternative approach, where the formaldehyde donors could be identified in Part 1 of the SUSMP as a corollary to the definition of 'free formaldehyde"? If so, what specific wording would achieve that outcome?
- None of the seven named 'formaldehyde donors' appear to be listed in the Schedules under a synonym or different name, but can this be guaranteed?

- No specific uses in Australian products have been identified in the NICNAS IMAP report, but there are a number of potential uses in consumer products (cosmetics, adhesives, cleaners, paints) in products overseas. Is there sufficient information on potential uses to apply all the scheduling restrictions of formaldehyde to the seven listed formaldehyde donors?
- The ACCS might note that the restrictions placed on these seven formaldehyde donors by international cosmetics and other regulations range from concentration limits to unlimited approvals.

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *formaldehyde donors*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1123

Scheduling status

Formaldehyde donors are not specifically scheduled.

Similar chemical groups, namely formaldehyde and paraformaldehyde, are listed in Schedules 2 and 6 and Appendices C and E. The formaldehyde's scheduling status mirrors the paraformaldehyde's schedule status; therefore, paraformaldehyde's scheduling status is not provided.

Free formaldehyde is listed in Part 1, Interpretation.

Furthermore, formaldehyde is cross-referenced to metacresolsulphonic acid and formaldehyde condensation product. Metacresolsulphonic acid and formaldehyde condensation product are listed in Schedule 6 (all concentrations for the treatment of animals) and Appendix F (Safety Directions 1 'Avoid contact with eyes' and 4 'Avoid contact with skin'.)

Methylene glycol is cross-referenced to free formaldehyde and formaldehyde.

Formaldehyde's scheduling status is provided below.

Schedule 2

FORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

b) in other preparations containing 0.2 per cent or less of free formaldehyde.'

Schedule 6

FORMALDEHYDE (excluding its derivatives) in preparations containing 0.05 per cent or more of free formaldehyde **except**:

a) for human therapeutic use;

b) in oral hygiene preparations;

c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement: protect cuticles with grease or oil;

e) in all other cosmetic preparations; or

f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: contains formaldehyde.

Appendix C

FORMALDEHYDE (excluding its derivatives):

a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde except in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: contains formaldehyde.

Appendix E

Poison	Standard Statement
Formaldehyde (see also paraformaldehyde)	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800764 766) or a doctor (at once). G3 - If swallowed, do NOT induce vomiting. E2 - If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes. R1 - If inhaled, remove from contaminated area. Apply artificial respiration if not breathing. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Part 1, Interpretation

"Free formaldehyde" includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol.

Scheduling history

The formaldehyde donors have not been previously considered for scheduling.

Pre-meeting public submissions

Three submissions were received. One submission supported the proposal to cross-reference formaldehyde donors to formaldehyde in the in the index. Two submissions did not support cross-referencing formaldehyde donors to formaldehyde.

Summary of ACCS advice to the delegate

The committee recommended that Part 1, Interpretation of the SUSMP be amended to include formaldehyde donors.

The committee supported the implementation date of 1 June 2015.

As this amendment is for clarity, not a scheduling decision, no reason under 52E(1) was required.

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 scheduling of formaldehyde is quite complex, with existing entries in Schedules 2 and 6, and in Appendices C and E, regulating the types of products where it may be used. There are also separate mirror entries for paraformaldehyde on the basis that it is converted in solution to formaldehyde. These entries include specific exemption concentrations where the potential for sensitising and skin/eye irritancy effects are appropriately controlled. The exemption cut-offs for these entries rely on defining the amount of free formaldehyde that is released in aqueous solutions. The February 2012 ACCS meeting recommended proposals to clarify the meaning of the definition 'free formaldehyde' in Part 1 of the SUSMP and this clarification included cross-referencing methylene glycol in the SUSMP index as the hydrated form of formaldehyde in aqueous solution.

In considering the referral of seven substances that can function as 'formaldehyde donors' the ACCS advice was that separate individual listings in the Schedules or Appendices was not the optimum way of regulating these substances via scheduling. One reason for this is that concentration cut-offs suitable for formaldehyde would not be appropriate for compounds of different molecular weights and that release different amounts of formaldehyde. The approach favoured by the ACCS was to amend the definition of 'free formaldehyde' in Part 1 of the SUSMP, so that the amount of formaldehyde released by these 'donors' would define the way in which they are regulated by the SUSMP. The delegate accepts this advice as a pragmatic way of extending controls over the use of substances that release formaldehyde and thereby present sensitisation and/or irritancy risks. The delegate also notes that this approach was endorsed by the European Union Scientific Committee on Cosmetic Products and Certain Non-Food Products intended for Consumers (SCCNFP) in a report (SCCNFP/586/02) referred in an industry pre-meeting consultation submission. The EU report addressed four of the seven substances assessed in the NICNAS IMAP report.

The ACCS considered, but did not support, the approach adopted for methylene glycol, whereby listing of the seven specified 'formaldehyde donors' in the SUSMP index would cross- reference their scheduling status with that of formaldehyde. The delegate notes that one pre-meeting industry submission did not support cross-referencing the seven 'formaldehyde donors' in the SUSMP index, but seeks further advice on whether such SUSMP index cross-referencing would assist with

understanding the extension of scheduling controls where these substances are used as formaldehyde donors or precursors.

The delegate has decided the implementation date 1 February 2016.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health i.e. clarity of controls.

Public submissions on the interim decision

One public submission was received, which supported the delegate's interim decision. The submission notes that they do not support cross-referencing of formaldehyde donors to the formaldehyde schedule entry; however, there is merit in considering some referencing to provide users of The Poisons Standard, that for formaldehyde donors, the formaldehyde schedule entry should be checked against the level of formaldehyde in the product.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision. The delegate notes the suggestion that there should be some advice to product manufacturers to check the concentration of free formaldehyde that could be released from 'formaldehyde donors' but that no pragmatic advice was given on how to achieve this via an amendment to the either formaldehyde entries in the SUSMP or to the Part 1 definition of 'free formaldehyde'. 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 February 2016.

Schedule entry

Part 1, Interpretation

"Free formaldehyde" includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol and formaldehyde released from formaldehyde donors.

1.3 Methylated spirit(s)

Scheduling proposal

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

- Based on advice received during consultation on the interim decision from the March 2014 ACCS meeting to develop suitable label statements to warn consumers of the fire risks associated with using methylated spirits to refill burners while alight or hot, the delegate determined that the interim decision be set aside. The delegate now proposes to seek further advice on the practicality of attaching the suggested warning statements to either/both the burners and/or the fuels. The delegate also notes that, under the current Schedule 5 entry for METHYLATED SPIRIT(S), some fuels would not be captured even if a warning statement were to be included in the schedule entry (e.g. those in containers containing 5 litres of more and those biofuels not meeting the current specification for methylated spirits). The delegate proposes to seek advice on which ingredients may be used to denature alcohol, in order to better align the SUSMP methylated spirits definition with current industry practice and to ensure that biofuels to which any warning statement would be applied are consistent with the wording of the Schedule 5 entry.

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

This was a delegate initiated scheduling matter.

In March 2014, the ACCS considered the delegate's referral for advice regarding a proposed label warning statement (stated below) alerting consumers regarding the serious burn hazard methylated spirit poses when refuelling ethanol burners.

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

In June 2014, the delegate made an interim decision not to include the requested warning statements by amending the current Schedule 5 entry for methylated spirit, nor by amending Part 2 Clause 7(h), nor by creating a specific Appendix F entry, and invited further submissions. A further submission was made in response to the delegate's interim decision, indicating that the efficacy of warning statement is a key factor in the development of effective and efficient responses to product hazards. The current warning statements do not address a specific hazard and individuals are being injured though lack of understanding of the nature of the risk. The submission requested that the delegate consider amending the current methylated spirit(s) entry to provide a prominent new warning statement as follows:

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

Delegate's reasons for referring this to the committee

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

The delegate asked the ACCS the following question:

- Please refer to the information under the heading 'Scheduling Proposal'.

Substance summary

Methylated sprit, which is also known as denatured ethanol, or denatured alcohol, is a clear, colourless, mobile liquid. It is miscible with water in all proportions[1]. Methylated spirit is mainly used as a fuel for spirit burners and camping stoves and also as a solvent for cleaning preparations.

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

[1] Safe handling and storage of methylated spirit. Department of Transport and Main Roads, Queensland

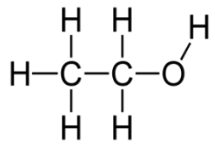

Figure 1. Structure of ethanol

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

Methylated spirit is classified as a Schedule 5 poison and the products' label includes the signal word "CAUTION". It is available from supermarkets, hardware stores and camping/outdoors stores. Safe Work Australia has classified methylated spirit as a hazardous substance. Methylated spirit is also classified as a dangerous good according to the criteria of the Australian Dangerous Goods (ADG) Code. The products' label includes the following information:

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

Since the introduction of ethanol burners into the Australian market, methylated spirit has also been used as a common fuel for these products. One product label was found to indicate (although not prominently) that the product is suitable for use as 'burner fuel' and provides instructions of use of filling the product into the burners. The labels of other brands were not found to have this information.

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

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

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

Scheduling status

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

Schedule 5

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

a) when included in preparations or admixtures; or

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

Appendix E

Poisons	Standard Statements
Methylated spirit	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). G3 - If swallowed, do NOT induce vomiting.

Part 2, Labels and Containers

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

Scheduling history

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

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

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

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

In August 2014, the delegate noted the serious nature of burns that have occurred through misuse of fuels that already have prominent flammability warnings and research on the proposed more explicit warning statement suggesting the potential for greater awareness of the dangers and possible preventive actions. The delegate decided to seek further information on the practicality of attaching the suggested warning statements to either/both the burners and/or the fuels. The delegate also noted that, under the current schedule 5 entry for METHYLATED SPIRIT(S), some fuels would not be captured even if a warning statement were to be included in the schedule entry (e.g. those in containers containing 5 litres of more and those biofuels not meeting the current specification for methylated spirit). The delegate had already noted the need to refer back to the ACCS the matter of which ingredients may be used to denature alcohol, and to better align the methylated spirit definition with current industry practice. Accordingly, the delegate decided to refer the matter back to the ACCS for further advice, and also to seek further input from industry and the Australian Competition and Consumer Commission (ACCC). This would include advice on the practicality of limiting the proposed warning statements to methylated spirit in products specifically packaged as biofuels for use in spirit burners and on the need to adjust the schedule entry so that warnings could be applied to the larger containers that are currently exempt from the Schedule 5 listing.

Pre-meeting public submissions

Two submissions were received.

One submission supports including nationally consistent warnings and extending the scope of the definition for methylated spirit to capture 'biofuels' and other types of methylated spirits using different combinations of denaturant and of removing the current Schedule 5 exemption for containers exceeding 5 litres.

The second submission did not support including additional warning statements on methylated spirits.

Summary of ACCS advice to the delegate

The committee recommended that a new Appendix F, Part 1 Warning Statement be created: 'WARNING: Do not attempt to refill burner while it is in use or still warm; it could lead to serious burn injury'.

The committee recommended that this new Appendix F, Part 3 Warning Statement be added for Methylated spirit(s).

The committee supported the implementation date of 1 February 2016.

The committee recommended that the current definition of methylated spirits remains appropriate.

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.

The reasons for the interim decision comprised the following:

- To mitigate the risk of serious burn injury accident.

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

This matter was initially referred to the March 2014 meeting of the ACCS, at which time the advice to the delegate was that flammability warnings on containers of methylated spirits provide sufficient warning of the risks associated with use as fuel for 'spirit burners' and that the specific additional and more specific and directive Warning Statement (*WARNING: DO NOT attempt to refill methylated spirit burner while it is in use or still warm; it could lead to serious burn injury or death*) should NOT be imposed via a new statement in the Appendix F entry for methylated spirits. The delegate accepted this recommendation, but arising from a further submission responding to the interim decision, decided to re-commit the matter for consideration at the November 2014 ACCS

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

One issue, highlighted in a pre-meeting industry submission to the November 2014 ACCS, was that warning statements on burners themselves would be more effective than labelling fuel containers, and that accidents associated with re-filling hot burners imply that some people simply ignore existing flammability and other warnings on container labels. Furthermore, methylated spirits have uses other than as biofuels, and to require the labelling of all containers with the specific Appendix F Warning Statement would be excessive.

The advice from the November 2014 ACCS meeting supported the development of a new Appendix F warning Statement, although the advice was not unanimous. The delegate accepts this advice and proposes a new Warning Statement (107. WARNING: Do not attempt to refill burner while it is in use or still warm; it could lead to serious burn injury) in Part 1 of Appendix F. The issue then arises whether it is appropriate to apply WS 107 to a new entry for methylated spirit in Appendix F.

One of the options considered (but not supported) by the ACCS was that a new Schedule 5 entry be created for methylated spirit when used specifically as a biofuel, and that the Appendix F WS be applied to only that entry. The delegate is attracted to this option because it restricts the application of WS 107 to the specific use for which it was developed. Furthermore, the new Schedule 5 entry could be broadened to cover methylated spirit that does not fit the definition of methylated spirit in the current Schedule 5 entry. The Schedule 5 entry for METHYLATED SPIRIT specifies that it is ethanol denatured with three specific denaturants (one or more?). This definition was, in part, developed to counter the potential for methylated spirit to be ingested as an alcohol substitute. Information provided to the ACCS indicates that methylated spirit currently available in commerce and defined by other legislation (e.g. the *Excise Act 2011*) may be denatured with a larger range of substances. Some of these products are packaged and labelled as 'biofuels' suitable for use in spirit burners. Therefore, it is possible that such packaging may avoid specific packaging and labelling required under the current Schedule 5 entry for methylated spirit. Since the ACCS declined to support amending the Schedule 5 definition of methylated spirit, the delegate proposes a new Schedule 5 entry, to which WS 107 would be required.

The delegate agrees with the implementation date 1 February 2016.

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

Public submissions on the interim decision

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

Delegate's final decision

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

The delegate has confirmed the proposed implementation date of 1 February 2016.

Schedule entry

Schedule 5 – New Entry

METHYLATED SPIRIT(S) when packed and labelled as a 'biofuel' suitable for use in 'spirit burners'.

Appendix F, Part 1 - New Statement

107. WARNING: Do not attempt to refill burner while it is in use or still warm; it could lead to serious burn injury.

Appendix F, Part 3 - New Entry

Poison	**Warning Statement**	**Standard Statement**
Methylated spirit(s) when packed and labelled as a 'biofuel' suitable for use in 'spirit burners'.	107. WARNING: Do not attempt to refill burner while it is in use or still warm; it could lead to serious burn injury'	

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)

SUMMARY OF DELEGATES' FINAL DECISIONS

Substance	**Final Decision**
Lemongrass oil	**Appendix B – Delete Entry** LEMONGRASS OIL **Schedule 5 – New Entry** LEMONGRASS OIL in cosmetic and household cleaning preparations **except** in preparations containing 5 per cent or less of 3,7-dimethyl-2,6-octadienal. Implementation date - 1 June 2015
Polihexanide	**Schedule 5 – Delete Entry** POLIHEXANIDE **except** in preparations containing 5 per cent or less of polihexanide. **Schedule 6 – New Entry** POLIHEXANIDE **except:** a) in preparations containing 5 per cent or less of polihexanide; or b) when packed and labelled for therapeutic use.

Substance	Final Decision
	Appendix E, Part 2 – New Entry POLIHEXANIDE - Standard Statements – E1 Implementation date - 1 June 2015

2.1 Lemongrass oil

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 delete the lemongrass oil entry from Appendix B and to develop a listing in Schedule 5 to complement the entry for 3,7-dimethyl-2-6,-octadienal and its isomers.

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

This item was initiated by the delegates as one of the outcomes foreshadowed in the delegates' interim decision on 3,7-dimethyl-2-6,-octadienal and its isomers.

In August 2014, the delegates indicated that, based on advice received from the November ACCS meeting and the July ACCS-ACMS meeting, an interim decision was made for a new listing in Schedule 5 for 3,7-DIMETHYL-2-6,-OCTADIENAL and its isomers, in cosmetic and household cleaning preparations except in preparations containing 5 per cent or less of 3,7-Dimethyl-2,6-octadienal isomers. The interim decision noted that since lemongrass oil can contain up to 90% of citral, there is a need to review the current Appendix B entry for lemongrass oil.

Delegates' reasons for referring this to the committee

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

The delegates asked the ACCS-ACMS the following question:

- Please refer to information under 'Scheduling proposal'.

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *citral and related compounds*. This report is available on from the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=92

Scheduling status

Lemongrass oil is listed in Appendix B.

Appendix B

Substance	Date of entry	Reason for listing	Area of use
LEMONGRASS OIL	Feb 2000	A – Low Toxicity	7 – General 7.1 – Any use

Lemongrass oil contains up to 90% of citral (3,7-dimethyl-2-6,-octadienal). In September 2014, the delegates made an interim decision to list 3,7-dimethyl-2-6,-octadienal and its isomers in cosmetic and household cleaning preparations except in preparations containing 5 per cent or less of 3,7-dimethyl-2-6,-octadienal isomers in Schedule 5. The delegates' final decision was published in October 2014.

Scheduling history

In February 2000, the NDPSC noted the Essential Oils Working Party's (EOWP) recommendation that lemongrass oil warrants scheduling controls. NDPSC considered the EOWP's recommendation and decided, however, that lemongrass oil did not require a schedule listing. The NDPSC noted that lemongrass oil consists mostly of citral (65 to 96%) and has an acute oral LD_{50} value in the rat in excess of 5 g/kg. Citral is an aldehyde and as such can result in skin irritation. Citral, however, is not as toxic as cinnamaldehyde. It has an oral LD_{50} of 4.96 g/kg in the rat. The NDPSC agreed that it would be unlikely that lemongrass oil would be a hazard, and skin irritation potential is probably of minor significance. For these reasons, exemption from scheduling for lemongrass oil was considered appropriate. The NDPSC indicated that the decision was based on the low acute oral toxicity of lemongrass oil in the rat and the absence of evidence of significant toxicity in humans.

In April 2014, the delegate made a decision to defer the scheduling of citral, neral and geranial, pending further consideration by the advisory committees, noting the information received on product types, concentrations used and the likely presence of these isomers in various essential oils.

In September 2014, the delegates, based on the advice from the joint ACCS-ACMS, made an interim decision to list 3,7-dimethyl-2-6,-octadienal isomers in Schedule 5 and the SUSMP Index. This interim decision was based on a toxicological profile that is consistent with SPF criteria for listing in Schedule 5, specifically the potential to cause skin irritation and sensitisation. The delegates also noted that some essential oils can contain varying amounts of 3,7-dimethyl-2,6-octadienal isomers, and this could result in the inadvertent capture of essential oils containing more than the 5% cut-off. The lemongrass oil, containing up to 90% citral, would be captured by the proposed Schedule 5 listing. The delegates therefore foreshadowed the removal of lemongrass oil from Appendix B, its listing in Schedule 5 with a 5% cut-off, and that industry comment be sought on any regulatory implications.

Public pre-meeting submissions

One submission was received, which supported scheduling of lemongrass oil in line with citral, neral and geranial.

Summary of ACCS-ACMS advice to the delegates

The committee recommended that the Appendix B lemongrass oil entry be deleted and a new Schedule 5 entry be created for cosmetic and household cleaning preparations containing more than 5% of 3,7-dimethyl-2,6-octadienal.

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:

- due to the risk of skin irritation and sensitisation from its citral content, lemongrass oil should not be included in Appendix B.

Delegates' considerations

The delegates 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.

Delegates' interim decision

The delegates accept the advice of the ACCS-ACMS to delete the current Appendix B entry for lemongrass oil and to create a new entry in Schedule 5 to cover cosmetic and household cleaning products, with an exemption level of 5%. The primary reason is to align the scheduling of lemongrass oil with the recently introduced Schedule 5 entry for 3,7-DIMETHYL-2-6,-OCTADIENAL and its isomers, one of which (citral) may be a component of lemongrass oil at up to 90%.

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*: (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, which supported the delegates' interim decision.

Delegates' final decision

The delegates note the submission 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 B – Delete Entry

Substance	Date of entry	Reason for listing	Area of use
LEMONGRASS OIL	Feb 2000	A – Low Toxicity	7 – General 7.1 – Any use

Schedule 5 – New Entry

LEMONGRASS OIL in cosmetic and household cleaning preparations **except** in preparations containing 5 per cent or less of 3,7-dimethyl-2,6-octadienal.

2.2 Polihexanide

Scheduling proposal

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

- To delete the current Schedule 5 polihexanide entry and create a new Schedule 6 entry. Consideration will also be given to whether the existing exemption for preparations containing 5% or less of polihexanide should be maintained, or transferred to a new listing in Schedule 5. Consideration will also be given to the need to amend the existing Appendix E safety directions for products not regulated by the APVMA.

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

In September 2014, the Office of Chemical Safety (OCS), based on the Australian Pesticides and Veterinary Medicines Authority's (APVMA) review on polihexanide, referred the following proposal to be considered by the delegates:

- A proposal to delete the current Schedule 5 polihexanide entry and create a new Schedule 6 entry for preparations containing more than 5% of polihexanide.

The reasons for the request are the use pattern of the polihexanide products, and that the chemical:

- has moderate to high acute oral toxicity (solid polihexanide has an acute oral LD_{50} value of 549 and 501, male and female respectively);
- is a severe eye irritant;
- is a moderate skin sensitiser at 20% and a mild skin sensitiser at 6%;
- generally presents a moderate hazard from repeated use, as indicated by the available repeat-dose oral toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity findings.

In June 2011, the APVMA released an updated report, 'polihexanide carcinogenicity: analysis of human health risk', based on an OCS evaluation on the carcinogenicity potential of polihexanide. The report indicated that polihexanide has a potential for carcinogenicity in whole-of life studies in rodents via the oral route, but only at high exposure levels that are unlikely to be encountered in

occupational or public settings. Negative results were obtained in an 80-week dermal study in mice. There were no carcinogenic effects on skin. The occurrence of haemangiosarcoma in the liver at the high dose in the dermal study was considered not to be treatment related as it was within historical controls. Polihexanide did not appear to be genotoxic. The OCS evaluation report did not regard carcinogenicity findings in rodents as a barrier to continuing registration of products containing polihexanide.

Delegates' reasons for referring this to the committee

The delegates' reason for referring this scheduling proposal to the ACCS-ACMS was that this is a re-scheduling proposal and the SPF suggests that such applications be referred to an advisory committee for advice. In addition, the delegates would appreciate advice from the ACCS-ACMS on issues relating to the potential carcinogenicity of polihexanide and its use in a range of products not regulated by the APVMA (therapeutic goods and biocidal components of other commercial products).

The delegates asked the ACCS-ACMS the following questions:

- Does the ACCS-ACMS agree that evaluation of the newer toxicity data supports rescheduling of polihexanide to Schedule 6?
- What advice does the ACCS-ACMS offer in relation to the current exemption from scheduling at 5% or less?
    - Would retention of the exemption allow the unscheduled use of polihexanide as an antiseptic in therapeutic goods?
    - Given the evidence of potential sensitisation at low concentrations, is it more appropriate for the Schedule 6 listing to exempt products to Schedule 5 when 5% or less?
- Does the ACCS-ACMS concur with the assessment of potential carcinogenicity undertaken by the OCS, APVMA and international agencies?
- Is there a need to review the Appendix E statements for products not regulated by the APVMA?

Substance summary

Polyhexamethylene biguanide hydrochloride (Polihexanide or PHMB) is a chemical biocide. It is used as an active ingredient in various preparations such as wet wipes, wound irrigation solutions, sterile dressings as well as disinfectants. Due to its excellent biocidal properties, its usage has increased in personal care products and pharmaceuticals, for instance in the treatment of chronic wounds and burns. This widely used biocide has been reviewed by the US EPA, which noted that the biocide has very low aggregate risk of adverse health effects to the public or environment, except for occupational users.

Polihexanide binds to the negatively charged phosphate head groups of phospholipids on the bacterial cell wall causing increased rigidity by sinking nonpolar segments into hydrophobic domains, and membrane disruption with subsequent cytoplasmic shedding, culminating in cell death. The antibacterial activity of polihexanide depends on its molecular structure. Minimum requirements for biocidal activity are met by having more than 2 biguanide moieties and 5-7 methylene groups as a spacer. Therefore, polihexanide represents an oligomeric substance with a number-average degree of polymerization of 2-5. It is a cationic biocide marketed worldwide, because of its excellent antimicrobial activity, chemical stability, low toxicity and reasonable cost. Polihexanide is highly soluble in water (20%, w/v) and aliphatic alcohols, but poorly soluble in nonpolar liquids. The biguanide moieties are strong bases and monoprotonated at a pH value of 7

(pKa1=2–3; pKa2=10.5–11.5) resulting in a polycation with a positive charge at each biguanide moiety[2].

Polihexanide is a polymer of chlorhexidine that is used as an antimicrobial for the control of microorganisms, algae and fungi in swimming pools and spas. It is also used as a disinfectant in veterinary products, and as a sanitiser for milk handling equipment. Polihexanide is also used as a biocide (disinfectant) in medical equipment, medical procedures, contact lens cleaners, food preparation surfaces, and industrial situations.

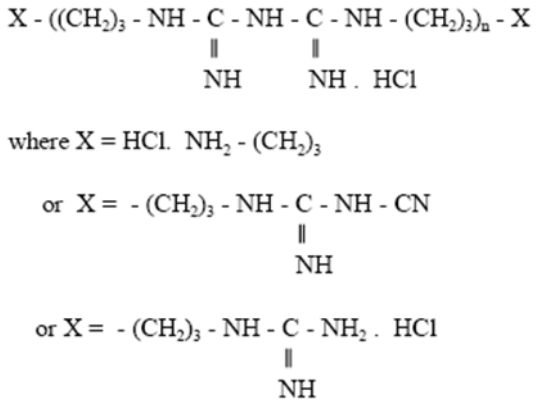

Figure 1. Structure of polihexanide

Acute toxicity

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

Toxicity	Species	Polihexanide	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	20% solution: 2747 (M), 2504 (F).	Low toxicity
		[PHMB equivalent: 549 (M), 501 (F), low]	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	20% solution: > 2000 (no deaths).	Low toxicity
		[PHMB equivalent: > 400 (no deaths)]	Low toxicity**
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Slight irritant	

[2] Markus Küsters, Sören Beyer, Stephan Kutscher, Harald Schlesinger and Michael Gerhartz. Rapid, simple and stability-indicating determination of polyhexamethylene biguanide in liquid and gel-like dosage forms by liquid chromatography with diode-array detection. Journal of Pharmaceutical Analysis, Volume 3, Issue 6, December 2013, Pages 408–414. Available at http://www.sciencedirect.com/science/article/pii/S2095177913000269.

Toxicity	Species	Polihexanide	SPF Classification
Eye irritation	Rabbit	Severe irritant	
Skin sensitisation (Guinea Pig Maximisation Test)	Guinea pig	20% solution: moderate 6% solution: mild	

* Polyhexamethylene biguanide hydrochloride (PHMB) is listed in the Poisons Standard as polihexanide.
**repeat dose dermal toxicity study showed no systemic effects up to 1500 mg/kg bw/d

Toxicity of the products

The toxicity data for the products were not available, so the toxicity was estimated by the OCS based on the available toxicity of the constituents and their respective concentrations in the products.

Pool/spa sanitisers containing 200 g/L polihexanide are expected to have:

- low oral toxicity
- low dermal toxicity
- slight skin irritancy
- severe eye irritancy
- skin sensitisation potential

The acute inhalational toxicity of these products is unknown due to the general lack of specific toxicological data on the active constituent and formulation excipients. This is not considered a significant data deficiency as the products are all liquids, which during use are poured and not sprayed, thus minimising the risk of inhalation.

Home veterinary topical products containing 0.3 g/L polihexanide and 54 g/L benzalkonium chloride are expected to have:

- low oral toxicity
- low dermal toxicity
- low inhalational toxicity
- low irritancy to the eye and skin
- skin sensitisation potential

Veterinary disinfectants containing 4 g/L polihexanide and 54 g/L benzalkonium chloride are expected to have:

- moderate oral toxicity
- low dermal toxicity
- low inhalational toxicity
- slight eye irritancy

- slight skin irritancy
- skin sensitisation potential

Trigene II Virucidal Disinfectant Concentrate containing 1g/L polihexanide, 75 g/L didecyl dimethyl ammonium chloride (DDAC) and 50 g/L benzalkonium chloride is expected to have:

- moderate oral toxicity
- low dermal toxicity
- low inhalational toxicity
- severe eye irritancy
- moderate skin irritancy
- skin sensitisation potential

Milking machine cleaner containing polihexanide and glycolic acid is expected to have:

- low oral toxicity
- low dermal toxicity
- low inhalational toxicity
- corrosive to the eye and skin
- skin sensitisation potential

Repeat-dose toxicity

Repeat-dose oral studies in mice, rats and dogs demonstrated that the target organ was the liver.

Liver effects in chronic studies in mice included hepatocyte hypertrophy, induction of hepatic DNA synthesis and increased pigmentation from 167 mg/kg bw/d and increased incidence of extramedullary haematopoiesis in the spleen at 715 mg/kg bw/d. In a chronic rat study, plasma ALP activity was increased in females at 162 mg/kg bw/d, and in a chronic dog study, increased plasma ALT, reduced cholesterol and liver histopathology was noted at 91 mg/kg bw/d. The tumours noted in these chronic studies are described in the carcinogenicity section below. Other effects noted in these studies include increased mortality and weight loss/reduced body weight gain in mice, rats and dogs, histopathological changes in the kidney, spleen and gall bladder of mice and in the testes of dogs.

In a 28-day repeat dose inhalation study in rats, a no observed effect level (NOEL) of 0.024 mg/m^3 was established based on histopathological changes in the larynx (squamous metaplasia).

In a short-term dermal study in mice (21-day), doses up to 200 mg/kg bw/d did not result in any systemic toxicity, although local dermal effects (erythema, oedema and scabbing) were noted from 60 mg/kg bw/d. A chronic dermal study in mice showed irritation to the skin, hyperkeratosis and desquamation only at much higher doses (30 mg/mouse, approximately 1500 mg/kg bw/d). Systemic effects were noted at this dose, including increased mortality, hepatotoxicity, bilateral protrusion of the eyes, and reduced body weight gain. In the chronic study, however, it was unclear if test sites were covered; therefore, oral ingestion cannot be ruled out.

Genotoxicity

There was no evidence of a genotoxic potential *in vitro,* with and without metabolic activation, or *in vivo*.

Carcinogenicity

Polihexanide was identified as a potential carcinogen in chronic oral rodent studies. In a chronic study in mice, haemangiosarcoma in the liver and squamous cell carcinoma at the recto-anal junction were noted at high exposure levels (approximately 700 to 850 mg/kg bw/d). The squamous cell carcinoma was considered to be a consequence of chronic irritation and subsequent inflammation. In a chronic rat study, 1/128 females had haemangiosarcoma in the liver and 4/128 had haemangioma in the liver at doses of approximately 120 to 160 mg/kg bw/d. As these tumours are rare in this strain of rat, it was considered possible that these tumours were treatment related. An expert review, however, concluded that these were only sporadic and not related to treatment, given (for example) the absence of pre-neoplastic findings.

Polihexanide is therefore associated with cancer in rodents but only at high doses, which are considered unlikely to be encountered in an occupational or public setting. In addition, polihexanide does not appear to be genotoxic, and a clear threshold for effect (NOEL) was demonstrated in carcinogenicity studies in both test species. Therefore, the OCS does not consider the observed tumours to be a likely health risk to humans from the continued use of polihexanide containing products.

Reproduction and developmental toxicity

Polihexanide did not cause reproductive toxicity in rats and there was no evidence of developmental effects in rats or rabbits. Increased incidence of extra ribs and skeletal variations of the sternebrae occurred in rat and rabbit studies respectively, but only at maternotoxic doses. Four rabbits were terminated due to abortion at the maternotoxic dose (severe weight loss) of 40 mg/kg bw/d polihexanide, but the abortions were considered secondary to maternal toxicity rather than a direct developmental effect.

Observation in humans

In a skin irritation study in human volunteers, a broad spectrum topical bactericide product containing polihexanide (other constituents unknown), was applied to a plaster and applied to the skin for 24 h. The doses tested were equivalent to 0.3%, 0.6% and 1% polihexanide. One out of 45 people tested developed a well-defined erythema at 1%. Two cases of severe anaphylaxis have been reported following contact of surgical wounds with a disinfectant containing 0.2% polihexanide. An immediate-type hypersensitivity reaction to polihexanide in both patients was suggested by positive intradermal injection tests. It appears that damage to the epidermal barrier or application to mucous membranes may have been a predisposing factor.

The prevalence of a polihexanide-induced skin sensitisation response was found to be extremely low (six out of 1554 patients or 0.4%), when patch-tested at a 2.5% strength on individuals with known contact allergen responses to cosmetics and medications.

Chlorhexidine is a widely used medical disinfectant known to cause allergic reactions including contact dermatitis and (less commonly) anaphylactic reactions when applied to the skin, or introduced into the body via catheters. As a polymer of chlorhexidine, the potential for polihexanide to cause similar type reactions cannot be excluded. The available evidence to date suggests that adverse reactions to commercial strength products containing polihexanide are possible but extremely uncommon. In Australia, there have been no reported cases of adverse reactions associated with the use of medical disinfectant and antiseptic products containing polihexanide or chlorhexidine.

Public exposure

Public exposure is expected from some products. Intentional and accidental exposure are expected during use of the home veterinary products (a shampoo and ointment) and exposure to the pool/spa products both during use and when bathing in treated water. The use of polihexanide containing pool/spa sanitisers will result in public exposure to polihexanide while bathing in treated pools and spas.

International regulations

No information provided. The Scheduling Secretariat has obtained the following:

In September 2004, the US Environmental Protection Authority (US EPA) determined that polihexanide is eligible for re-registration provided that additional required data confirm this decision, the risk mitigation measures outlined in the US EPA's document are adopted, and label amendments are made to reflect this measure.

In March 2014, the European Chemicals Agency (ECHA) review the inhalational toxicity potential of the substance and recommended *that "a classification Acute Tox 1– H330 (CLP), and T+; R26 (DSD) is warranted based on the results from the study by Carney (1976)."* This is in addition to the hazard classifications of Carc. 2, Acute Tox. 2, Acute Tox. 4, STOT RE 1, Eye Dam. 1 and Skin Sens. 1B.

Scheduling status

Polihexanide is currently listed in Schedule 5 and also included in Appendix F.

Schedule 5

POLIHEXANIDE **except** in preparations containing 5 per cent or less of polihexanide.

Appendix F

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

Scheduling history

In May 1977, the Poisons Schedule (Standing) Committee (PSC) considered the substance (at that time it was called poly (hexamethylene biguanide) hydrochloride) and decided to list it in Schedule 5 and Appendix A (now called Appendix E). The reason for these entries was its LD_{50} in the rat was 1 g/kg (toxicity end-point details were not provided).

In November 1982, the PSC considered an application requesting that preparations containing less than 20% of polihexanide be exempted from scheduling. The PSC did not accept the proposal because of concerns over "equivocal" results in developmental studies in rats, low survival rate in sub-acute oral studies in rats, and severe eye irritancy. The PSC, however, agreed to a 5% cut-off as

exempt from scheduling, on the basis that polihexanide was not a skin or eye irritant at that concentration.

In November 2000, the NDPSC decided to change the nomenclature of the Schedule 5 entry from poly (hexamethylene biguanide) hydrochloride to polihexanide. This decision was to reflect the World Health Organisation's decision to use the International Non-proprietary Name (INN).

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS-ACMS advice to the delegates

The committee recommended that the current Schedule 5 polihexanide entry be deleted and a new Schedule 6 entry be created for preparations containing more than 5% of polihexanide. The Committee also recommended that the new entry specifically exempt from scheduling preparations containing polihexanide when packed and labelled for therapeutic use. The committee also recommended that a First Aid Statement 'E1 – If in eyes wash out immediately with water' be applied.

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 (c) the toxicity of a substance.

The reasons for the recommendation comprised the following:

- In products for domestic use.
- Is a severe and irreversible eye irritant with moderate acute oral toxicity.

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS 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 delete the current Schedule 5 entry for POLYHEXANIDE and create a new entry in Schedule 6, with exemptions at 5% concentration and exempting therapeutic uses. The critical toxicological endpoints driving this categorisation (acute toxicity, severe skin/eye irritancy and sensitisation potential) are consistent with SPF criteria for listing in Schedule 6, with the public health risk sufficiently ameliorated for products under 5 per cent. The delegates also accept the ACCS/ACMS recommendation that products packed and labelled for therapeutic use should be specifically exempted.

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: 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.

Delegates' final decision

The delegates 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 5 – Delete

POLIHEXANIDE **except** in preparations containing 5 per cent or less of polihexanide.

Schedule 6 – New Entry

POLIHEXANIDE **except:**

a) in preparations containing 5 per cent or less of polihexanide; or

b) when packed and labelled for therapeutic use.

Appendix E, Part 2 – New Entry

Poison	**Standard statements**
Polihexanide	E1 – If in eyes wash out immediately with water.