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

February 2015

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

A delegate of the Secretary to the Department of Health hereby gives notice of the delegate's interim decisions for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* – SUSMP) under subsection 42ZCZP 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 delegate's interim 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 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/industry/scheduling-submissions.htm.

Interim decisions

This notice provides the interim decisions of the delegate, the reasons for those decisions and invites further submissions from the applicant and parties who made valid submissions in response to the original invitations for submissions. Further submissions must be relevant to the proposed amendment, must address a matter mentioned in section 52E of the *Therapeutic Goods Act 1989* and be received by the closing date **19 February 2015.**

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

Please note that all valid submissions received on or before the closing date will be published following removal of confidential information. It is up to the person making the submissions to highlight any information which they wish to be considered as confidential. Material claimed to be commercial-in-confidence will be considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the *Scheduling Policy Framework for Medicines and Chemicals* (the SPF). The SPF is accessible at https://www.tga.gov.au/publication/ncctg-scheduling-policy-framework.

Persons making submissions are strongly encouraged to lodge submissions in electronic format (word or unsecured PDF preferred) via the email address Chemicals.Scheduling@health.gov.au.

The closing date for further submissions is **19 February 2015**.

Privacy and your personal information

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

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

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

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

The Department's privacy policy is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/privacy-policy. Alternatively you may contact the Department by telephone on (02) 6289 1555 or freecall 1800 020 103, or by using the online inquiries form at www.health.gov.au.

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 and in a hardcopy Amendment 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 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* http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf
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 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[1];
- 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.

Schedule entry

Appendix C – New Entry

DI(METHYLOXYETHYL) PHTHALATE for cosmetic use.

Appendix C – New Entry

DIISOBUTYL PHTHALATE for cosmetic use.

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

1.2 1,4-Benzenediamine, 2-nitro

Scheduling proposal

The delegate referred the following scheduling proposal for consideration by the 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 1 June 2015 / 1 October 2015 / 1 February 2016.

In August 2014, NICNAS, under the 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.

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.	

Poison	Warning statement	Standard statement
• 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.

1.3 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 statements	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.

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.

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

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[2].

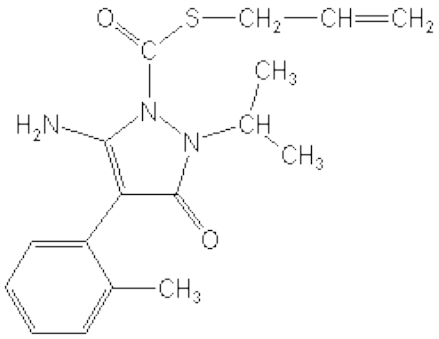

Figure 1. Structure of fenpyrazamine

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	

[2] 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

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 LC_{50} ($mg/m^3/4h$)	Rat	> 5612 (no deaths)	Low toxicity
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 air blast 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.

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[3].

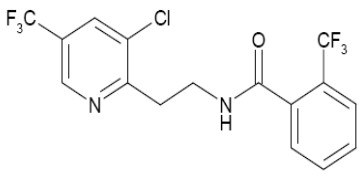

Figure 2. Structure of fluopyram

[3] 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.

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 (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	> 5112	Low toxicity
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	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.

Schedule entry

Schedule 5 – New Entry

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

1.8 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 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 metacresoluslphonic acid and formaldehyde condensation product. Metacresoluslphonic 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.

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

1.9 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 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 questions.

- 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[4]. 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.

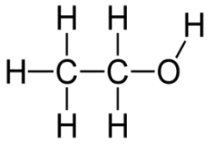

Figure 3. Structure of ethanol

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

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

- 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

Poison	Standard statement
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.

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'	

1.10 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[5], 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[6].

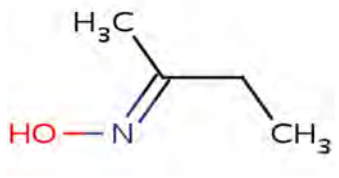

Figure 4. Structure of MEKO.

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 toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Non-irritant	
Skin sensitisation (closed patch test)	Guinea pig	Non-sensitiser	

[5] 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].

[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].

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)[7].

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[8]

[7] 2-Butanone, oxime (Butanone oxime). Health Canada. Available at [http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=32AD1FD8-1#a11].
[8] 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)[9]

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

Poison	Standard statement
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.

[9] 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.

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.