Australian Government
Department of Health
Therapeutic Goods Administration

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

4 February 2016

(ACCS and ACMS meetings – November 2015)

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

A delegate of the Secretary to the Department of Health hereby gives notice of 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 subsections 42ZCZP the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (the implementation date) of the decision.

The delegate's interim decisions and reasons relate to:

- scheduling proposals initially referred to the November 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#15); and
- scheduling proposals initially referred to the November 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS#16).

Pre-meeting public notice

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 9 October 2015 on the TGA website at: Public notice about scheduling.

Redacted versions of public submissions received in response to ACCS items were published on 8 January 2016 at: Public submissions on scheduling matters. Redacted versions of public submissions received in response to ACMS items will be published on or after the date of this notice.

Interim decisions

This notice provides the interim decisions of the delegates, 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 (published on 6 August 2015 and 9 October 2015 for general scheduling applications and for AgVet and delegate-initiated scheduling application respectively at https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-medicines-acms-meeting-november-2015 and https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-accs-and-acms-meetings-

november-2015). Edited versions of these submissions are available at https://www.tga.gov.au/public-submissions-scheduling-matters.

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 18 February 2016.

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* (SPF, 2015), issued by the Australian Health Ministers' Advisory Council (AHMAC). The SPF is accessible at: AHMAC - Scheduling policy framework for medicines and chemicals.

Persons making submissions are strongly encouraged to lodge submissions in electronic format (word or unsecured PDF preferred) via the email address provided below. Submissions, preferably in electronic format, should be made to:

> Chemicals.Scheduling@health.gov.au for items referred to the Advisory Committee on Chemicals Scheduling; and
>
> Medicines.Scheduling@tga.gov.au for items referred to the Advisory Committee on Medicines Scheduling.

The closing date for further submissions is 18 February 2016.

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 purposes 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 the submissions.

The consequences 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 on the Department of Health website.

Alternatively, you may contact the Department by telephone on 02 6289 1555 or freecall 1800 020 103, or by using the online enquiries form.

Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

Abbreviation	Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network

Abbreviation	Name
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name
ISO	International Standards Organization
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])

Abbreviation	Name
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted flow insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities

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

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

1. Scheduling proposals referred to the November 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#15)

Summary of delegate's interim decisions

Substance	Interim decision
1,3-Dichloropropene	***Schedule 7—Amend Entry*** 1,3-DICHLOROPROPENE **except** in biocidal preparations containing 0.3 per cent or less of 1,3-dichloropropene. Proposed implementation date: 1 June 2016.
1,5-Naphthalenediol	***Schedule 6—New Entry*** 1,5-NAPHTHALENEDIOL **except**: a) in non-oxidative hair dye preparations containing 1 per cent or less of 1,5-naphthalenediol 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 sensitisation 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 b) in oxidative hair dye preparations containing 1 per cent or less of 1,5-naphthalenediol after mixing under oxidative conditions 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 sensitisation 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. ***Appendix E—New Entry*** 1,5-NAPHTHALENEDIOL Part 1, Standard Statements: A, E1, S1

Substance	Interim decision
	Appendix F—New Entry 1,5-NAPHTHALENEDIOL Part 1, Warning Statement: 28 Part 2, Safety Directions: 1 Proposed implementation date: 1 October 2016.
1-Naphthol	***Schedule 6—New Entry*** 1-NAPHTHOL **except** in hair dye preparations containing 1 per cent or less of 1-naphthol after mixing under oxidative conditions 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 sensitisation 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. ***Appendix E—New Entry*** 1-NAPHTHOL Part 1: Standard Statements: A, E1, S1 ***Appendix F—New Entry*** 1-NAPHTHOL Part 1: Warning Statement: 28 Part 2: Safety Directions: 1 Proposed implementation date: 1 October 2016.
2,6-Dimethoxy-3,5-pyridinediamine	***Schedule 6—New Entry*** 2,6-DIMETHOXY-3,5-PYRIDINEDIAMINE **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 0.25 per cent or less of 2,6-dimethoxy-3,5-pyridinediamine after mixing for use 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 sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

Substance	Interim decision
	Written in letters not less than 1.5 mm in height. ***Appendix F—New Entry*** 2,6-DIMETHOXY-3,5-PYRIDINEDIAMINE Part 1, Warning Statement: 28 Proposed implementation date: 1 October 2016.
2,7-Naphthalenediol	***Schedule 6—New Entry*** 2,7-NAPHTHALENEDIOL **except**: a) in non-oxidative hair dye preparations containing 1 per cent or less of 2,7-naphthalenediol 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 sensitisation 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 b) in oxidative hair dye preparations containing 1 per cent or less of 2,7-naphthalenediol after mixing under oxidative conditions 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 sensitisation 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. ***Appendix E—New Entry*** 2,7-NAPHTHALENEDIOL Part 1: Standard Statements: A, E1, S1 ***Appendix F—New Entry*** 2,7-NAPHTHALENEDIOL Part 1: Warning Statement: 28 Part 2: Safety Directions: 1, 3 Proposed implementation date: 1 October 2016.

Substance	Interim decision
4-Amino-3-nitrophenol	***Schedule 6—New Entry*** 4-AMINO-3-NITROPHENOL **except**: a) in non-oxidative hair dye preparations and eyebrow/eyelash colouring products containing 1 per cent or less of 4-amino-3-nitrophenol 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 sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. Written in letters not less than 1.5 mm in height; or b) in oxidative hair dye preparations and eyebrow/eyelash colouring products containing 1 per cent or less of 4-amino-3-nitrophenol after mixing under oxidative conditions 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 sensitisation to certain individuals. 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 E—New Entry*** 4-AMINO-3-NITROPHENOL Part 1: Standard Statements: A ***Appendix F—New Entry*** 4-AMINO-3-NITROPHENOL Part 1: Warning Statement: 28 Proposed implementation date: 1 October 2016.
Amisulbrom	***Schedule 5—New Entry*** AMISULBROM Proposed implementation date: 1 June 2016.
C.I. Direct Orange 1 And an editorial of the C.I. Acid Black 29 entry to	***Schedule 7—Amend Entry*** BENZIDINE-BASED AZO DYES

Substance	Interim decision
include CAS number.	· 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) · C.I. Direct Orange 1 (CAS No. 54579-28-1) · 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'-

Substance	Interim decision
	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) Proposed implementation date: 1 June 2016.
Azo dyes (not listed on AICS)	***Schedule 7—Amend Entry*** AZO DYES that are derivatives by diazotisation of any of the following substances: · *o*-anisidine (CAS No. 90-04-0) · *o*-toluidine (CAS No. 95-53-4) · *p*-aminoazobenzene (CAS No. 60-09-3) · *o*-aminoazotoluene (CAS No. 97-56-3) · 2,4-toluenediamine (CAS No. 95-80-7) · 5-nitro-*o*-toluidine (CAS No. 99-55-8) · *p*-chloroaniline (CAS No. 106-47-8) · 2-naphthylamine (CAS No. 91-59-8) · 2,4,5-trimethylaniline (CAS No. 137-17-7) · 6-methoxy-*m*-toluidine (*p*-cresidine) (CAS No. 120-71-8) Proposed implementation date: 1 June 2016.
Isethionate, as mixed ammonium and ethanolamine salts of 2-hydroxyethanesulfonic acid	***Appendix B—New Entry*** ISETHIONATE, as mixed ammonium and ethanolamine salts of 2-hydroxyethanesulfonic acid Part 1 – Reasons for Entry a) Low toxicity and b) use pattern restricts hazard Part 2 - Area of Use 1.11 Adjuvant in agricultural products. Proposed date for addition to SUSMP: 1 June 2016.
1-(1,1-Dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene (musk ambrette)	***Schedule 10—New Entry*** 1-(1,1-DIMETHYLETHYL)-2-METHOXY-4-METHYL-3,5-DINITROBENZENE (musk ambrette)

Substance	Interim decision
	Cross reference entry in Index: Amber Musk Proposed implementation date: 1 June 2016.
Oxathiapiprolin	***Appendix B—New Entry*** OXATHIAPIPROLIN Part 1 –Reasons for Entry c) Low toxicity Part 2 – Area of Use 1.3 Fungicide. Proposed date for addition to SUSMP: 1 June 2016.
p-Methylaminophenol	***Schedule 6—New Entry*** *p*-METHYLAMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of *p*-methylaminophenol after mixing for use 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 sensitisation to certain individuals. 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 F—New Entry*** *p*-METHYLAMINOPHENOL Part 1, Warning Statement: 28 Proposed implementation date: 1 October 2016.
Schedule 5 Paint Labelling Amendment	The delegate has decided to defer making a decision on this issue, pending formal consultation with the States/Territories, as required in the new AHMAC Scheduling Policy Framework for amendments to Parts 1-3 of the Poisons Standard.
Topramezone	***Schedule 5—New Entry*** TOPRAMEZONE Proposed implementation date: 1 June 2016.

1.1 1,3-Dichloropropene

Scheduling proposal

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

- In August 2015, the delegate received a request to consider amending an entry for 1,3-dichloropropene in Schedule 7 of the SUSMP to allow for 0.3 per cent or less in biocidal formulations.

Scheduling application

The reasons for the request were:

- The applicant suggested it to be extremely difficult and not economically feasible to remove 1,3-dichloropropene to non-detectable levels after the production process from the antimicrobial products CTAS and cis-CTAC.
- In the CTAC and *cis*-CTAC production process, 1,3-dichloropropene , one of the raw materials, is added in slight excess to ensure the complete reaction of other raw materials. Removal of the excess 1,3-dichloropropene is to a level of less than 0.3% in the final CTAC product. To reduce the level of 1,3-dichloropropene in the final product to a consistently non-detectable level would require additional processing steps and/or equipment addition to the current production process, and would not be economically feasible for continued long-term manufacture of the product.
- The reasons outlined by the applicant for the request to down-schedule 1,3-dichloropropene are those of an economic nature and that the antimicrobial products CTAC and *cis*-CTAC, of which 1,3-dichloropropene is requested to be exempt from scheduling, are compliant to EU and US regulations. The consumables that CTAC and *cis*-CTAC are present in are quite broad, ranging from detergents, floor waxes and polishes, adhesives, construction materials, paints, inks, latex emulsions, metalworking fluids, and spinning fluids for textiles, as well as paper and paperboard packaging for dry foods. There is no outline of human health risks in their request, that is, the potential consequences that a down-scheduling of 1,3-dichloropropene may pose to human health.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS support the applicant's proposal to create an exemption cut-off of 0.3% in the current Schedule 7 entry for 1,3-dichloropropene?
- Should such an exemption be limited to its presence as an impurity in the specific substances mentioned in the applicant's submission; namely methanamine-3-chloroallylochloride (CTAC and *cis*-CTAC), or should it apply more broadly to biocidal products?
- What weight should be given to the applicant's advice that CTAC and *cis*-CTAC containing up to 0.3% 1,3-dichlorpropene are compliant with EU and US regulations?
- In Part 1, there is a general, exemption from the schedules when substances are present at a concentration below 10 mg/kg (0.001%). However, this exemption does not apply to substances listed in Schedule 7.
- Appendix G provides for low level exemptions for substances, including some Schedule 7 substances such as arsenic, selenium (although there are additional exemptions in sub-clauses of their S7 entries). Would listing of 1,3-dichloropropene in Appendix G be an alternative to amending the Schedule 7 entry?

Substance summary

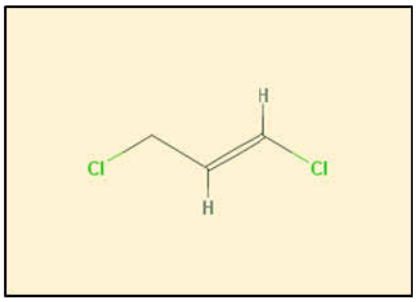


Figure 1: Structure of 1,3-dichloropropene

No toxicity profile was on 1,3-dichloropropene nor the active ingredients CTAC and *cis*-CTAC by the applicant. The following information was extracted from NICNAS and Safe Work Australia websites.

An Environmental Health Criteria report on 1,3-dichloropropene can be found here at IPCS INCHEM.

Hazard classification

1,3-Dichloropropene is classified as hazardous, with the following risk phrases for human health in the HSIS:

- T; R24/25 (acute toxicity);
- Xn; R20–65 (acute toxicity, aspiration hazard); and
- Xi; R36/37/38 (irritation).

Acute toxicity

No information provided by the applicant.

Repeat-dose toxicity

No information provided by the applicant.

Mutagenicity

No information provided by the applicant.

Genotoxicity

No information provided by the applicant.

Carcinogenicity

No information provided by the applicant.

1,3-Dichloropropene is listed in IARC Group 2B (possibly carcinogenic to humans) carcinogens.

Safe Work Australia place 1,3-dichloropropene as a Category 3 carcinogen. Substances suspected of having carcinogenic potential are those substances which have possible carcinogenic effects on humans but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal or epidemiological studies, but this is insufficient to place the substance in Category 2.

1.1 Animal studies

Technical-grade dichloropropene (containing 1% epichlorohydrin) was administered to mice and rats. Dose-related increases in the incidences of tumours of the urinary bladder, lung and fore stomach were observed in mice. In male rats, dose-related increases in the incidences of benign and malignant

fore stomach tumours and benign liver tumours were reported; in female rats, benign fore stomach tumours were found.

In one study of subcutaneous administration in female mice, the cis isomers produced malignant tumours at the site of injection. However, skin application of the cis isomers to mice has not produced any conclusive results.

The International Agency for Research on Cancer (IARC) has reviewed many animal inhalation studies, but failed to demonstrate a relationship between inhalation exposure and tumour production.

1.2 Human studies

Two case reports of human malignancy were reviewed by the IARC. There are no epidemiological studies of human carcinogenicity known to the Exposure Standards Working Group.

2. Conclusion

Technical-grade dichloropropene (containing 1% epichlorohydrin) is carcinogenic to experimental animals through oral administration. Carcinogenicity of dichloropropene through inhalation has not been demonstrated in animals.

There is inadequate evidence for carcinogenicity of dichloropropene in humans.

3. Recommendation for carcinogen category

After reviewing the relevant data, the Exposure Standards Working Group is of the view that dichloropropene may have carcinogenic potential to humans, based on the limited evidence from animal studies, but the available information is not adequate for making a satisfactory assessment. The Working Group recommends that dichloropropene be classified as Category 3 carcinogen (Substance Suspected of having Carcinogenic Potential). The reader is encouraged to review the section on Carcinogens in the Guidance Note on the Interpretation of Exposure Standards for Atmospheric Contaminants in the Occupational Environment, for guidance on the classification system of carcinogens.

Reproduction and developmental toxicity

No information provided by the applicant.

Observation in humans

No information provided by the applicant.

Public exposure

No information provided by the applicant.

NICNAS IMAP states 1,3-dichloropropene has an exposure standard of 4.5 mg/m^3 (1 ppm) time weighted average (TWA) (Galleria Chemica).

International regulations

The applicant outlined in their proposal that their antimicrobial CTAC and cis-CTAC substances, of which 1,3-dichloropropene is a product of their manufacture, are compliant to international regulations in the EU and USA. The international regulations for 1,3-dichloropropene, the substance in question, were not provided. These are outlined below.

1,3-dichloropropene is listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

A TWA of 4–5 mg/m^3 (1 ppm) in Canada, Denmark, Iceland, Norway, and the USA, and 0.5 mg/m^3 (0.11 ppm) in Germany and Switzerland.

A STEL of 50 mg/m^3 (10 ppm) in Ireland and South Africa, and 2 ppm in Canada (Saskatchewan).

Scheduling status

1,3-Dichloropropene is currently listed in Schedule 7 and Appendix J.

Appendix J, Part 2

Poisons	Standard Statements
1,3-dichloropropene	Condition 1: Not to be available except to authorised or licensed persons.

Scheduling history

1,3-Dichloropropene was previously marketed in Australia but its withdrawal by the sponsor (Dow Chemical (Australia) Ltd) was notified to the PACC in 1987, due to recommendations by the Committee, that it would cease its sale and distribution in Australia of Telone II, which comprised 91% of 1,3-dichloropropene. Prior to 1994, commercial formulations included up to 1% of the known genotoxic carcinogen, epichlorohydrin, while post-1994 commercial formulations have included epoxidised soybean oil as a stabiliser.

In November 2000, at the #29 NDPSC meeting, Dow Agrosciences Australia Ltd had submitted data in support of the technical grade active constituent 1,3-dichloropropene and the registration of two end-use-products Telone® Soil Fumigant (1140g/L) and Telone® C-35 Soil Fumigant (825g/L + chloropicrin 460g/L). These products were proposed for use by professional and accredited fumigators in the treatment of a range of soil borne diseases, nematodes, wireworms and other plant parasites as a pre-planting soil fumigant. The proposal was to delete the Appendix J entry and reschedule 1,3-dichloropropene to Schedule 6. This proposal was not supported by the Committee who decided that the current Schedule 7 and Appendix J entries for 1,3-dichloropropene were to remain appropriate. This was made in part due to the Committee noting that the proposed use was limited to accredited fumigators and that this could be enforced as a Restricted Chemical Product (NRA registration) in some jurisdictions. However, other jurisdictions had no legislative mechanism apart from Schedule 7/Appendix J to enforce such controls over use. It was in addition, noted that the request for rescheduling had arisen as a consequence of the new toxicology evaluation and had not been requested by the company.

Pre-meeting public submissions

No public submission was received.

ACCS advice to the delegate

The Committee recommended that the Schedule 7 entry for 1,3-dichloropropene be amended as follows:

Schedule 7—Amend Entry

1,3-DICHLOROPROPENE except when in biocidal formulations at 0.3 per cent or less.

The committee recommended an implementation date 1 June 2016.

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; (c) the toxicity of a substance.

The reasons for the recommendations comprised the following:

- manufacturing impurity in biocide and low risk to human health at concentrations of 0.3% or less in biocides

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[1];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to accept the advice of the Committee and amend the Schedule 7 entry of 1,3-dichloropropene.

The proposed implementation date is **1 June 2016**.

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 the substance.

Schedule entry

Schedule 7—Amend Entry

1,3-DICHLOROPROPENE **except** in biocidal preparations containing 0.3 per cent or less of 1,3-dichloropropene.

1.2 1,5-Naphthalenediol

Scheduling proposal

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

- To create a new entry for 1,5-naphthalenediol in Schedule 6 to include use in hair dyes and eyelash containing products with an appropriate cut-off.

Scheduling application

- In August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) assessment programme, referred the proposal to be considered by the delegate for inclusion in the Poisons Standard.

The reasons for the request were:

- The chemical has reported cosmetic use in permanent hair dye preparations in Australia;
- The chemical is a moderate to strong skin sensitiser; and

[1] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

- The overseas restrictions for use of this chemical in hair dyes (the maximum concentration allowed in an oxidative hair dye substance is 1 % or 0.5 % when used in combination with hydrogen peroxide).
- The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of sensitisation even below the overseas restriction cut-off, the risk would be better controlled by inclusion of warning statements on the labels of preparations containing the chemical below the concentration cut-off. This chemical has similar use and hazard profiles to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 1,5-napthalenediol (acute toxicity, negative mutagenicity and sensitisation potential) warrants controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of moderate to severe skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including 1,5-naphthalenediol in Schedules 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 1%, as suggested in the NICNAS report? Should this cut-off be adjusted to 0.5% when in combination with hydrogen peroxide?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Given that there may be some commercial uses other than in cosmetics, should a Schedule 6 listing be specific for use in hair dyes or cosmetic products (as for some other hair dye ingredients)?
- What name should be used for any schedule entry – 1,5-naphthalendiol or 1,5-dihydroxynaphalene?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for 1,5-napthalenediol. This report is publicly available on the NICNAS website.

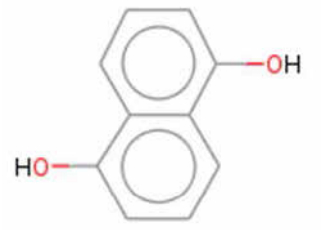


Figure 2. Chemical structure of 1,5-napthalenediol

Acute toxicity

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

Toxicity	Species	1,5-naphthalenediol	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	660 or >2000	Schedule 5 or 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	—
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	—
Skin irritation	Rabbit	Mild irritant	Schedule 5
Eye irritation	Rabbit	Irritant	Schedule 5
Skin sensitisation (local lymph node assay)	Mice	Moderate to severe skin sensitiser (EC3 = 3.4 %)	Schedule 6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Sensitisation

A local lymph node assay (LLNA) was performed according to the Organisation of Economic Co-operation and Development test guideline (skin sensitisation) using female CBA/J mice. Various concentrations of 1,5-naphthalenediol were assessed across two experiments. The following stimulation index (SI) values were generated for these concentrations (% / SI): 0.25 / 1.4; 1 / 2.5; 2.5 / 2.8; 5 / 18.4; 25 / 16.7; 50 / 6.1. The estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 3.4 %. Therefore, under these test conditions, 1,5-naphthalenediol was found to be a moderate to severe skin sensitiser.

Repeat-dose toxicity

Based on the data available, the chemical is not expected to cause serious damage to health from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation routes.

Genotoxicity

Based on the negative results observed in several in vivo genotoxicity studies, the chemical is not expected to be genotoxic.

Carcinogenicity

No data are available.

Reproduction and developmental toxicity

Based on the available data, the chemical is not expected to have developmental toxicity. No data are available on reproductive toxicity.

Public exposure

The chemical is reported to be used in oxidative hair dye preparations in Australia. Internationally, the chemical is reported to be used in oxidative and non-oxidative hair dye preparations.

Following a safety evaluation, the Scientific Committee on Consumer Products (SCCP) (2010) concluded that "1,5-naphthalenediol, as an ingredient in oxidative and non-oxidative hair dye formulations; at a maximum on-head concentration of 1 % does not pose a risk to the health of the consumer, apart from its sensitising potential."

Currently, there are no restrictions in Australia on using this chemical in cosmetics/hair dyes or eyelash colouring products. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk to public under the uses identified.

International regulations

Many countries, including New Zealand, the European Union (EU) and the Association of Southeast Asian Nations (ASEAN) have restricted the use of this chemical in cosmetics.

The chemical is listed on the following:

- EU Cosmetics Regulation 344/2013 Annex III—List of Substances which cosmetic products must not contain except subject to the restrictions laid down (maximum authorised concentration in the finished cosmetic product is 1.0 % or 0.5 % when used in combination with hydrogen peroxide);
- New Zealand Cosmetic Products Group Standard—Schedule 5 Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- The ASEAN Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

In the EU, it is mandated that products containing the chemical at any concentration have warning labels indicating that the product can be allergenic.

Scheduling status

N/A

Scheduling history

1,5-naphthalenediol has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received.

No objections to aligning with EU were raised. It was noted in the submission that it is important to maintain "in-use" concentrations for hair dye preparations, due to the mode of use being mixing with an oxidising substance prior to use.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that new Schedule 6, Appendix E and Appendix F entries be created for 1,5-naphthalenediol with exemptions and cut-offs as follows:

Schedule 6—New Entry

1,5-NAPHTHALENEDIOL except:

a) in non-oxidative hair dye preparations containing 1 per cent or less 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 sensitisation 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

b) in oxidative hair dye preparations containing 1 per cent or less after mixing under oxidative conditions 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 sensitisation 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.

Appendix E—New Entry

1,5-NAPHTHALENEDIOL

Part 1, Standard Statements: A, E1, S1

Appendix F—New Entry

1,5-NAPHTHALENEDIOL

Part 1, Warning Statement: 28

Part 2, Safety Directions: 1

The committee recommended an implementation date of 1 June 2016.

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

The reasons for the recommendations comprised the following:

· The substance is used in hair dye products

· The substance is a moderate skin sensitiser and therefore meets the criteria for inclusion in Schedule 6

Delegate's considerations

The delegate considered the following in regards to this proposal:

· Scheduling proposal;

· Public submissions received;

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

Delegate's interim decision

The delegate's interim decision is to create new Schedule 6, with appropriate exemption and cut-off, Appendix E and Appendix F entries for 1,5-naphthalenediol.

Oxidative hair dyes of the aromatic diamine and aminophenolic classes have some common toxicological properties that warrant controls over scheduling. These features are primarily skin-eye irritancy and sensitization potential. These toxicological properties generally align with SPF criteria for listing in Schedule 6. Several of these dyes (e.g. phenylenediamines, toluenediamines; aminophenols) have already been listed in Schedule 6, but previous scheduling policies have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitization, and recommending testing for individual susceptibility before use. This approach is commonly called 'reverse scheduling'. Where there is potential mutagenicity, or the need to prevent uses for skin colouration (tattooing) or use to dye eyebrows or eyelashes, some of these substances have been listed in Schedule 10 to prevent such uses.

This is one of six oxidant hair dyes that were referred to the November 2015 meeting of the ACCS for advice to the delegate on scheduling. The key issues were whether their toxicological profiles sufficiently match the SPF criteria for inclusion in Schedule 6 and whether product exemptions based on 'reverse scheduling' could be applied, consistent with labelling provisions applied to other oxidative hair dyes. Given that some products containing oxidative hair dyes require mixing with an oxidant, such as hydrogen peroxide, before application to the hair, consideration was given to appropriate exemption cut-off concentrations that take account of the final concentration applied to the hair.

The delegate notes, and accepts, ACCS advice that 1,5-naphthalenediol should be listed in Schedule 6, with an exemption cut-off at 1%, provided products are labelled with the warning statements about potential skin/eye irritation and sensitisation that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that the potential for eye irritation requires warning statements relating to use for dyeing eyebrows and eyelashes. The INCI name (1,5-naphthalenediol) is the preferred name for listing in the Schedules.

The proposed implementation date is **1 October 2016**.

A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

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

Schedule entry

Schedule 6—New Entry

1,5-NAPHTHALENEDIOL except:

[2] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

a) in non-oxidative hair dye preparations containing 1 per cent or less of 1,5-naphthalenediol 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 sensitisation 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

b) in oxidative hair dye preparations containing 1 per cent or less of 1,5-naphthalenediol after mixing under oxidative conditions 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 sensitisation 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.

Appendix E—New Entry

1,5-NAPHTHALENEDIOL

Part 1, Standard Statements: A, E1, S1

Appendix F—New Entry

1,5-NAPHTHALENEDIOL

Part 1, Warning Statement: 28

Part 2, Safety Directions: 1

1.3 1-Naphthol

Scheduling proposal

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

· To create a new entry for 1-naphthol in Schedule 6 to include use in hair dyes and eyelash colouring products with an appropriate cut-off.

Scheduling application

On the 28th August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the following proposal to be considered by the delegate for inclusion in the Poisons Standard:

The reasons for the request are:

· the chemical has reported cosmetic use in permanent hair dye preparations in Australia;

· the chemical is a strong skin sensitiser;

- the chemical is a skin and eye irritant;
- the chemical has moderate acute dermal toxicity;
- only limited data are available on acute inhalation toxicity and no data on repeated dose inhalation toxicity; and
- the overseas restrictions for use of this chemical in hair dyes state that the maximum concentration allowed in an oxidative hair dye substance is 1.0 % after mixing with hydrogen peroxide.
- The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of skin sensitisation even below the allowed overseas concentration cut-off, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical below the concentration cut-off. The chemical has similar use and hazard profiles to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 1-napthalenol (acute toxicity, negative mutagenicity and sensitisation potential) warrants controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of severe skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including 1-naphthol in Schedules 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 2%, as suggested in the NICNAS report? Should this cut-off be adjusted to 1% when in combination with hydrogen peroxide?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Given that there may be some commercial uses other than in cosmetics, should a Schedule 6 listing be specific for use in hair dyes or cosmetic products (as for some other hair dye ingredients)?
- What name should be used for any schedule entry – 1-naphthalenol or 1-napthol, alpha-naphthol or 1-hydroxynaphalene?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report 1-naphthalenol and its related compounds. This report is publicly available on the NICNAS website.

Acute toxicity

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

Toxicity	Species	1-naphthol	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1870	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	880	Schedule 6
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	>0.097 (limited data)	N/A
Skin irritation	Rabbit	Irritant	Schedule 5
Eye irritation	Rabbit	Severe irritant	Schedule 6
Skin sensitisation (LLNA)	Mouse	Skin sensitiser (EC3 = 1.3 %)	Schedule 6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Skin sensitisation

Based on the available data, the chemical is a strong skin sensitiser.

In a local lymph node assay (LNNA) conducted according to the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 429, the chemical at 0.1, 0.25, 0.5, 1 or 2.5 % was applied topically to the ventral and dorsal surfaces of the ears of 18 female CBA/J mice. The mean stimulation indices were 1.4, 1.0, 1.2, 1.5 and 8.5, respectively, for the 0.1, 0.25, 0.5, 1 and 2.5 % concentrations. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 1.3 %, indicating a strong sensitisation potential.

In a guinea pig maximisation test, both intradermal and topical induction used 0.1 % aqueous solutions of the chemical. Two weeks after topical induction, the animals were challenged by an occlusive dermal application of 0.05 % or 0.1 % of the chemical for 24 hours. No skin reaction was observed in this study. However, it should be noted that the concentration of the chemical used in this study was considered to be too low to clearly characterise the sensitisation potential of the chemical.

In an open epicutaneous test, a 3 % dilution of the chemical was applied onto the shaved flank skin of Pirbright white guinea pigs for six days/week for three weeks. Two weeks later a single challenge dose was applied to the opposite flank skin. No skin reaction was observed in the animal.

Repeat-dose toxicity

Based on the available data, the chemical is not expected to cause serious damage to health from repeated oral and dermal exposure. No information was available on repeated dose inhalation toxicity.

Genotoxicity

Based on the available data from in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

Carcinogenicity

Limited data are available. The chemical at 0.5 % concentration was not carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemical is not expected to cause reproductive and developmental toxicity.

Public exposure

The chemical is reported to be used in permanent hair dye preparations in Australia. Internationally, the chemical is used in oxidative hair dyes.

The Association of South East Asian Nations (ASEAN), Canada, New Zealand and the European Union (EU) have restricted the use of this chemical in cosmetics. Following a safety evaluation, the Scientific Committee on Consumer Products concluded that 'apart from the risks associated with the use of a strong sensitiser, the use of the chemical itself in oxidative hair dye formulations at a maximum concentration of 2.0 % on the head, does not pose any other risk to the health of the consumer'.

Currently, there are no restrictions in Australia on using this chemical in cosmetic products. In the absence of any regulatory controls, the characterised critical health effects (particularly skin sensitisation) have the potential to pose an unreasonable risk to the public given the identified uses.

International regulations

The chemical is listed on the following:

- ASEAN Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: 'after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 2.0%';
- EU Regulation (EC) No 344/2013 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1 % calculated as free base';
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: '(a) the maximum authorised concentration in the finished cosmetic product is 2.0%; and (b) in combination with hydrogen peroxide the maximum use concentration upon application is 1.0%'; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

In the EU, it is mandated that products containing the chemical at any concentration have warning labels indicating that the product can be allergenic.

Scheduling status

N/A

Scheduling history

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

Pre-meeting public submissions

One public submission was received. No objections to aligning with the EU requirements were raised. It was noted however that it is important to maintain "in-use" concentrations for hair dye preps, due to the mode of use being mixing with an oxidising substance prior to use.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that new Schedule 6, Appendix E and Appendix F entries be created for 1-naphthol with appropriate cut-offs and exemptions as follows:

Schedule 6—New Entry

1-NAPHTHOL except in hair dye containing 1 per cent or less after mixing under oxidative conditions 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 sensitisation 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.

Appendix E—New Entry

1-NAPHTHOL

Part 1: Standard Statements: A, E1, S1

Appendix F—New Entry

1-NAPHTHOL

Part 1: Warning Statement: 28

Part 2: Safety Directions: 1

The committee recommended an implementation date of 1 June 2016.

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

The reasons for the recommendations comprised the following:

- The substance is used in hair dye products
- The substance has acute oral and dermal toxicity and is a strong skin sensitiser, a skin irritant and moderate to severe eye irritant and meets the criteria for inclusion in Schedule 6

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

- Scheduling factors[3];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create new Schedule 6, with appropriate exemption and cut-off, Appendix E and Appendix F entries for 1-naphthol.

Oxidative hair dyes of the aromatic diamine and aminophenolic classes have some common toxicological properties that warrant controls over scheduling. These features are primarily skin-eye irritancy and sensitization potential. These toxicological properties generally align with SPF criteria for listing in Schedule 6. Several of these dyes (e.g. phenylenediamines, toluenediamines; aminophenols) have already been listed in Schedule 6, but previous scheduling policies have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitization, and recommending testing for individual susceptibility before use. This approach is commonly called 'reverse scheduling'. Where there is potential mutagenicity, or the need to prevent uses for skin colouration (tattooing) or use to dye eyebrows or eyelashes, some of these substances have been listed in Schedule 10 to prevent such uses.

This is one of six oxidant hair dyes that were referred to the November 2015 meeting of the ACCS for advice to the delegate on scheduling. The key issues were whether their toxicological profiles sufficiently match the SPF criteria for inclusion in Schedule 6 and whether product exemptions based on 'reverse scheduling' could be applied, consistent with labelling provisions applied to other oxidative hair dyes. Given that some products containing oxidative hair dyes require mixing with an oxidant, such as hydrogen peroxide, before application to the hair, consideration was given to appropriate exemption cut-off concentrations that take account of the final concentration applied to the hair.

The delegate notes, and accepts, ACCS advice that 1-napthol should be listed in Schedule 6, with an exemption cut-off at 1%, provided products are labelled with the warning statements about potential skin/eye irritation and sensitisation that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that the potential for severe eye irritation requires warning statements relating to use for dyeing eyebrows and eyelashes. The INCI name (1-naphthol) is the preferred name for listing in the Schedules.

The proposed implementation date is **1 October 2016**.

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

Schedule entry

Schedule 6—New Entry

1-NAPHTHOL **except** in hair dye preparations containing 1 per cent or less of 1-naphthol after mixing under oxidative conditions 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 sensitisation to certain individuals. A preliminary test according to the accompanying directions should be

[3] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

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.

Appendix E—New Entry

1-NAPHTHOL

Part 1: Standard Statements: A, E1, S1

Appendix F—New Entry

1-NAPHTHOL

Part 1: Warning Statement: 28

Part 2: Safety Directions: 1

1.4 2,6-Dimethoxy-3,5-pyridinediamine

Scheduling proposal

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

- To create a new entry for 2,6-dimethoxy-3,5-pyridinediamine in Schedule 6 to include use in hair dyes with an appropriate cut-off.

Scheduling application

In August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) assessment programme, referred the proposal to be considered by the delegate for inclusion in the Poisons Standard.

The reasons for the request were:

- The chemical has reported cosmetic use in permanent hair dye preparations in Australia;
- The chemical has high acute oral toxicity;
- The chemical is a moderate to severe skin sensitiser;
- Severe health effects observed in rats during repeated oral exposure; and
- The overseas restrictions for use of this chemical in hair dyes (the maximum concentration allowed in a hair dye substance is 0.25 % after mixing with hydrogen peroxide.
- The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of sensitisation below the overseas concentration cut-off, the risk would be better controlled by inclusion of warning statements on the label of hair dye formulations containing the chemicals below the cut-off concentration. The chemical has similar use and hazard profile to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 2,6-dimethoxy-3,5-pyridinediamine (acute toxicity, negative mutagenicity, skin-eye irritancy and moderate-severe sensitisation potential) warrants controls over use in cosmetics and consumer products?

- What weight should be given to the evidence of moderate-severe skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including 2,6-dimethoxy-3,5-pyridinediamine in Schedules 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 0.5% (EU regulation) or 0.25% when in combination with hydrogen peroxide? Should there be no cut-off, based on the sensitisation potential?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Although there are no notified commercial uses other than in cosmetics, should a Schedule 6 listing be specific for use in hair dyes or cosmetic products (as for some other hair dye ingredients)?
- What name should be used for any schedule entry – 2,6-dimethoxy-3,5-pyridinediamine or 3,5-diamino-2,6-dimethoxypyridine?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

This report, containing more detailed information about the substance, is publicly available on the NICNAS website.

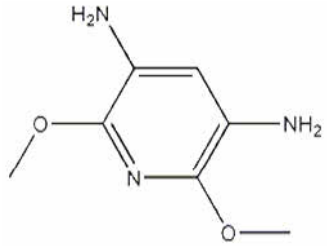


Figure 3. Chemical structure of 2,6-dimethoxy-3,5-pyridinediamine

Acute toxicity

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

Toxicity	Species	2,6-dimethoxy-3,5-pyridinediamine	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	187.5	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	-
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	-
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Guinea pig	Not irritating at 3 % concentration (limited data)	N/A
Skin sensitisation (LLNA)	Mouse	Skin sensitiser	Schedule 6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Skin sensitisation

The chemical is a moderate to severe skin sensitiser.

In the local lymph node assay (LLNA), female CBA/J mice (n = 5/group) were topically treated with 0.25 µL of the chemical at 0, 0.5, 1.5, 5.0 and 10.0 % concentrations (w/v) in dimethyl sulfoxide (DMSO) or in water/acetone (1:1) mixed with olive oil (4:1), once a day for three days (Organisation for Economic Co-operation and Development test guideline. The lymphoproliferation response, determined by the incorporation of (3H)-methyl thymidine was greater than the stimulation index (SI) threshold of three for concentrations ^{3}1.5 % in DMSO (SI = 3.6, 4.5 and 4.2 for 1.5, 5 and 10 % concentrations, respectively). The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated as 1.25 % in DMSO. The SI was greater than three only at the 10 % concentration in a mixture of water/acetone (1:1) mixed with olive oil (4:1), with a calculated EC3 of 6.88 %. Both treatments indicated the chemical was a skin sensitiser.

In a Magnusson–Kligman maximisation study, female Dunkin Hartley guinea pigs (n = 20) were intradermally injected with the chemical (0.1 mL of a 1 % solution) in sterile water. Freund's complete adjuvant was also injected. On day seven after being injected, the animals were topically treated with 10 % sodium lauryl sulfate in petrolatum to induce slight inflammation and enhance potential absorption. On day eight, the animals were topically treated with the chemical (0.5 mL of a 75 % solution) under occlusive conditions for 24 hours. The animals were challenged on days 22 and 29 with 0.2 mL of a 75 % aqueous solution. A slight increase in skin fold thickness, compared with the vehicle control group, was observed during the challenge. Skin reactions were observed in 55 % and 45 % of the animals at 24 and 48 hours after challenge, respectively, indicating that the chemical is a skin sensitiser.

Repeat-dose toxicity

Based on the treatment-related effects reported in the 90-day study in rats, the chemical is considered to cause serious damage to health from repeated oral exposure. A no observed adverse effect level (NOAEL) of 5 mg/kg bw/day was established based on the effects observed at 15 mg/kg bw/day (significantly decreased blood glucose and creatine levels; significantly decreased absolute liver and kidney weights in females; enlarged cervical lymph nodes; and treatment related changes in the liver (necrosis, mononuclear cell foci), lungs (pneumonitis) and oesophagus (epithelial hyperplasia and hyperkeratosis).

Genotoxicity

Based on the negative results reported for all in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

Carcinogenicity

Based on the available genotoxicity data, mechanistic considerations and mitigating factors of the chemical structure, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

No reproductive toxicity data are available. The chemical is not expected to have developmental toxicity.

Public exposure

The chemical is reported to be used in permanent hair dye preparations in Australia. The chemical has reported international use in oxidative hair dye products.

Currently, there are no restrictions in Australia on using this chemical in cosmetics or hair dyes. In the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses.

International regulations

Many countries including Canada, New Zealand, and the European Union (EU) have restricted the use of this chemical in cosmetics.

The chemical is listed on the following:

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III Part 2—List of substances provisionally allowed;
- European Union (EU) Cosmetics Regulation 344/2013—Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down (After mixing under oxidative conditions the maximum concentration applied to hair must not exceed 0,25 % (as hydrochloride));
- New Zealand Cosmetic Products Group Standard—Schedule 5: Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down (no details available);
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist"); and
- In CosIng, under wording of conditions of use and warnings, the chemical is stated as 'Can cause allergic reaction'.

Scheduling status

2,6-dimethoxy-3,5-pyridinediamine is not specifically scheduled.

Scheduling history

2,6-dimethoxy-3,5-pyridinediamine has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. No objections to aligning with the EU requirements were raised. It was noted however, that it is important to maintain "in-use" concentrations for hair dye preparations, due to the mode of use being mixing with an oxidising substance prior to use.

The public submission is available at the TGA website.

ACCS advice to the delegate

The committee recommended that a new Schedule 6 and Appendix F entries be created for 2,6-dimethoxy-3,5-pyridinediamine with appropriate exemptions or cut-offs as follows:

Schedule 6—New Entry

2,6-DIMETHOXY-3,5-PYRIDINEDIAMINE except when used in hair dye and eyebrow/eyelash colouring products at a concentration of 0.25 per cent or less after mixing for use 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 sensitisation to certain individuals. 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 F—New Entry

2,6-DIMETHOXY-3,5-PYRIDINEDIAMINE

Part 1, Warning Statement: 28

The committee recommended an implementation date of 1 June 2016.

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

The reasons for the recommendations comprised the following:

- The substance is used in hair dye products
- The substance has potential for strong sensitisation and acute toxicity and therefore meets the criteria for entry in Schedule 6
- Use at low concentrations can be managed by reverse scheduling labelling requirements in hair dyes

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 the substance.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[4];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create new Schedule 6, with appropriate exemption and cut-off, and Appendix F entries for 2,6-dimethoxy-3,5-pyridinediamine.

Oxidative hair dyes of the aromatic diamine and aminophenolic classes have some common toxicological properties that warrant controls over scheduling. These features are primarily skin-eye irritancy and sensitization potential. These toxicological properties generally align with SPF criteria for listing in Schedule 6. Several of these dyes (e.g. phenylenediamines, toluenediamines; aminophenols) have already been listed in Schedule 6, but previous scheduling policies have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitization, and recommending testing for individual susceptibility before use. This approach is commonly called 'reverse scheduling'. Where there is potential mutagenicity, or the need to prevent uses for skin colouration (tattooing) or use to dye eyebrows or eyelashes, some of these substances have been listed in Schedule 10 to prevent such uses.

[4] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

This is one of six oxidant hair dyes that were referred to the November 2015 meeting of the ACCS for advice to the delegate on scheduling. The key issues were whether their toxicological profiles sufficiently match the SPF criteria for inclusion in Schedule 6 and whether product exemptions based on 'reverse scheduling' could be applied, consistent with labelling provisions applied to other oxidative hair dyes. Given that some products containing oxidative hair dyes require mixing with an oxidant, such as hydrogen peroxide, before application to the hair, consideration was given to appropriate exemption cut-off concentrations that take account of the final concentration applied to the hair.

The delegate notes, and accepts, ACCS advice that 2,6-dimethoxy-3,5-pyridinediamine should be listed in Schedule 6, with an exemption cut-off at 0.25%, provided products are labelled with the warning statements about potential skin sensitisation that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that warning statements relating to use for dyeing eyebrows and eyelashes are not needed, because the substance is not a strong eye irritant.

The proposed implementation date is **1 October 2016**.

A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

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

Schedule entry

Schedule 6—New Entry

2,6-DIMETHOXY-3,5-PYRIDINEDIAMINE **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 0.25 per cent or less of 2,6-dimethoxy-3,5-pyridinediamine after mixing for use 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 sensitisation to certain individuals. 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 F—New Entry

2,6-DIMETHOXY-3,5-PYRIDINEDIAMINE

Part 1, Warning Statement: 28

1.5 2,7-Naphthalenediol

Scheduling proposal

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

- To create a new entry for 2,7-naphthalenediol in Schedule 6 to include use in hair dyes and eyelash colouring products with an appropriate cut-off.

Scheduling application

In April 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the proposal to be considered by the delegate for inclusion in the Poisons Standard.

The reasons for the request were:

- the chemical has reported cosmetic use in permanent hair dye preparations in Australia;
- the chemical is a moderate skin sensitiser;
- the chemical is a severe eye irritant;
- lack of data on acute or repeated dose dermal and inhalation toxicity; and
- the overseas restrictions for use of this chemical in hair dyes state that the maximum concentration allowed in an oxidative hair dye substance is 1.0 % after mixing with hydrogen peroxide.

The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of skin sensitisation even below the allowed overseas concentration cut-off, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical below the concentration cut-off. The chemical has similar use and hazard profiles to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 2,7-napthalenediol (acute toxicity, negative mutagenicity, skin-eye irritancy and sensitisation potential) warrants controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of moderate skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including 2,7-naphthalenediol in Schedules 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 1%, as suggested in the NICNAS report? Should this cut-off be the same when in combination with hydrogen peroxide?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Although there are no notified commercial uses other than in cosmetics, should a Schedule 6 listing be specific for use in hair dyes or cosmetic products (as for some other hair dye ingredients)?
- What name should be used for any schedule entry – 2,7-naphthalendiol or 2,7-dihydroxynaphalene?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report for 2,7-napthalenediol and its related compounds. This report is publically available on the NICNAS website.

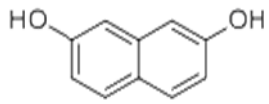


Figure 4. Chemical structure of 2,7-naphthalenediol

Acute toxicity

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

Toxicity	Species	2,7-naphthalenediol	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	2160	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	Rabbit	Not an irritant	N/A
Eye irritation	Rabbit	Severe irritant	Schedule 6
Skin sensitisation (LLNA)	Mouse	Skin sensitiser (EC3 = 2.8 %)	Schedule 6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Skin sensitisation

Based on the available data, the chemical is a moderate to strong skin sensitiser.

In a local lymph node assay (LLNA) conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline, the chemical, in a 4:1 mixture of acetone and olive oil, was applied to the dorsal surface of both ear lobes of female CBA/CaOlaHsd mice (five animals/group) once daily for three consecutive days. The chemical at test concentrations of 0.5, 1, 2.5, 5, 25 or 50 % produced stimulation indices (SIs) of 1.6, 1.8, 1.4, 4.5, 12.4 or 4.2, respectively. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 2.8 %, indicating moderate skin sensitisation potential.

Repeat-dose toxicity

Based on the available data, the chemical is not expected to cause serious damage to health from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation routes.

Genotoxicity

Based on the available data from in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical.

Reproduction and developmental toxicity

Based on the limited available data, the chemical is not expected to cause reproductive and developmental toxicity.

Public exposure

The chemical is reported to be used in permanent hair dye preparations in Australia. It has use overseas in both oxidative and non-oxidative preparations.

The Association of South East Asian Nations (ASEAN), European Union (EU) and New Zealand have restricted the use of this chemical in cosmetics. Following a safety evaluation, the Scientific Committee on Consumer Safety concluded that the chemical 'as an ingredient in oxidative and non-oxidative hair dye formulations at a maximum on-head concentration of 1% does not pose a risk to the health of the consumer, apart from its sensitising potential'.

Currently, there are no restrictions in Australia for using this chemical in cosmetic products. In the absence of any regulatory controls, the characterised critical health effects, particularly skin sensitisation, have the potential to pose an unreasonable risk to the public given the identified uses.

International regulations

The chemical is listed on the following:

- ASEAN Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: '(a) the maximum authorised concentration in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 1.0%; and (b) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.0%';
- EU Regulation (EC) No 344/2013 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: '(a) the maximum concentration in ready for use preparation is 1.0 %; and (b) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.0 %; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: '(a) the maximum authorised concentration in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 1.0%; and (b) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.0%'.

In the EU, it is mandated that products containing the chemical at any concentration have warning labels indicating that the product can be allergenic.

Scheduling status

N/A

Scheduling history

2,7-naphthalenediol has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. No objections to aligning with the EU requirements were raised. It was noted however that it is important to maintain "in-use" concentrations for hair dye preps, due to the mode of use being mixing with an oxidising substance prior to use.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that new Schedule 6, Appendix E and Appendix F entries be created for 2,7-naphalenediol as follows:

Schedule 6—New Entry

2,7-NAPHTHALENEDIOL except:

a) in non-oxidative hair dye preparations containing 1 per cent or less 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 sensitisation 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

b) in oxidative hair dye preparations containing 1 per cent or less after mixing under oxidative conditions 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 sensitisation 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.

Appendix E—New Entry

2,7-NAPHTHALENEDIOL

Part 1: Standard Statements: A, E1, S1

Appendix F—New Entry

2,7-NAPHTHALENEDIOL

Part 1: Warning Statement: 28

Part 2: Safety Directions: 1, 3

The committee recommended an implementation date of 1 June 2016.

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 the substance.

The reasons for the recommendation comprised the following:

- The substance is used in hair dye products
- The substance is a severe eye irritant and is a moderate skin sensitiser and therefore meets the criteria for inclusion in Schedule 6

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is accept the advice of the Committee and create new Schedule 6, with appropriate exemption and cut-off, Appendix E and Appendix F entries for 2,7-naphthalenediol.

Oxidative hair dyes of the aromatic diamine and aminophenolic classes have some common toxicological properties that warrant controls over scheduling. These features are primarily skin-eye irritancy and sensitization potential. These toxicological properties generally align with SPF criteria for listing in Schedule 6. Several of these dyes (e.g. phenylenediamines, toluenediamines; aminophenols) have already been listed in Schedule 6, but previous scheduling policies have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitization, and recommending testing for individual susceptibility before use. This approach is commonly called 'reverse scheduling'. Where there is potential mutagenicity, or the need to prevent uses for skin colouration (tattooing) or use to dye eyebrows or eyelashes, some of these substances have been listed in Schedule 10 to prevent such uses.

This is one of six oxidant hair dyes that were referred to the November 2015 meeting of the ACCS for advice to the delegate on scheduling. The key issues were whether their toxicological profiles sufficiently match the SPF criteria for inclusion in Schedule 6 and whether product exemptions based on 'reverse scheduling' could be applied, consistent with labelling provisions applied to other oxidative hair dyes. Given that some products containing oxidative hair dyes require mixing with an oxidant, such as hydrogen peroxide, before application to the hair, consideration was given to appropriate exemption cut-off concentrations that take account of the final concentration applied to the hair.

The delegate notes, and accepts, ACCS advice that 2,7-naphalenediol should be listed in Schedule 6, with an exemption cut-off at 1%, provided products are labelled with the warning statements about potential skin/eye irritation and sensitisation that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that the potential for severe eye irritation requires warning statements relating to use for dyeing eyebrows and eyelashes.

The proposed implementation date is **1 October 2016**.

A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

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

[5] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Schedule entry

Schedule 6—New Entry

2,7-NAPHTHALENEDIOL **except**:

a) in non-oxidative hair dye preparations containing 1 per cent or less of 2,7-naphthalenediol 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 sensitisation 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

b) in oxidative hair dye preparations containing 1 per cent or less of 2,7-naphthalenediol after mixing under oxidative conditions 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 sensitisation 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.

Appendix E—New Entry

2,7-NAPHTHALENEDIOL

Part 1: Standard Statements: A, E1, S1

Appendix F—New Entry

2,7-NAPHTHALENEDIOL

Part 1: Warning Statement: 28

Part 2: Safety Directions: 1, 3

1.6 4-Amino-3-nitrophenol

Scheduling proposal

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

· To create a new entry for 4-amino-3-nitrophenol in Schedule 6 to include use in hair dyes and eyelash colouring products with an appropriate cut-off.

Scheduling application

In August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the following proposal to be considered by the delegate:

The reasons for the request were:

- the chemical is used in permanent hair dye preparations in Australia;
- the chemical is a severe skin sensitiser; and
- the overseas restrictions for use of this chemical in cosmetics.
- The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of sensitisation below the concentration cut-off, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical below the concentration cut-off. This chemical has a similar use and hazard profile to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 4-amino-3-nitrophenol (acute toxicity, equivocal mutagenicity, skin-eye irritancy and strong sensitisation potential) warrants controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of strong skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including 4-amino-3-nitrophenol in Schedules 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 1%, as suggested in the NICNAS report, or 3% as recommended in the SCCP report? Should there be no cut-off on the basis of the strong sensitisation potential?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Although there are no notified commercial uses other than in cosmetics, should a Schedule 6 listing be specific for use in hair dyes or cosmetic products (as for some other hair dye ingredients)?
- What name should be used for any schedule entry – 4-amino-3-nitrophenol; 3-nitro-4-aminophenol; 1-hydroxy-3-nitro-4-aminobenzene or 2-nitro-4-hydroxyaniline?
- Would this substance be covered (as a derivative) by the current generic Schedule 6 entry for - NITROPHENOLS, ortho, meta and para except when separately specified in these schedules?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products? Note that there is a current Appendix F requirement for statements 1,4, and 8 for nitrophenols covered by the generic S6 entry?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report for 4-amino-3-nitrophenol and its related compounds. This report is publically available on the NICNAS website.

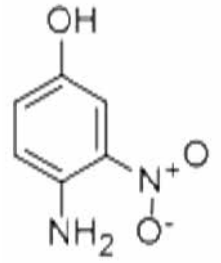


Figure 5. Chemical structure of 4-amino-3-nitrophenol

Acute toxicity

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

Toxicity	Species	4-amino-3-nitrophenol	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	500 –1000	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	–
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	–
Skin irritation	Rabbit	Not irritating at 6 % concentration (limited data)	–
Eye irritation	Rabbit	Irritating	Schedule 5
Skin sensitisation (LLNA)	Mouse	Severe skin sensitiser (EC3 = 0.2 %)	Schedule 6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Sensitisation

Based on the data available, the chemical is considered to be a severe skin sensitiser.

In a local lymph node assay (LLNA) test, groups of female CBA/J mice were topically treated with 25 µL of the chemical (in an acetone/olive oil mixture) at 0.05, 0.1, 0.5, 1 or 2.5 % concentrations, once daily for three days. The lympho-proliferation response, determined by the incorporation of (3H)-methyl thymidine exceeded the threshold of three (stimulation index (SI) >3) at concentrations >0.5 %. The estimated concentration needed to produce three-fold increase in lymphocyte proliferation (EC3) was calculated to be 0.2 %, indicating the chemical to be a severe skin sensitiser.

Repeat-dose toxicity

Based on the data available, the chemical is not considered to cause serious damage to health from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation routes.

Genotoxicity

Based on the negative in vivo genotoxicity data, the chemical is not considered to be genotoxic. However, it was reported that the data available are insufficient to exclude potential gene mutation.

Carcinogenicity

Based on the available genotoxicity data, mechanistic considerations and mitigating factors of the chemical structure, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

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

Public exposure

The chemical is reported to be used in permanent hair dye preparations in Australia. Internationally, the chemical is used in oxidative and non-oxidative hair dyes.

Currently, there are no restrictions in Australia on using this chemical in cosmetics or hair dye products. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk for the uses identified.

International regulations

Many countries, including New Zealand and the EU, have restricted the use of this chemical in cosmetics.

The chemical is listed on the following:

- EU Regulation (EC) No 344/2013 Annex III: List of Substances which cosmetic products must not contain except subject to the restrictions and conditions laid down

  Product type: (a) Hair dye substance in oxidative hair dye products (b) Hair dye substance in non-oxidative hair dye products

  Maximum concentration in ready for use preparation: (b) 1.0 %

  Other: (a) After mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.5 %;

- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to restrictions and conditions laid down; and

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 2 List of substances provisionally allowed.

In the EU, it is mandated that products containing the chemical at any concentration have warning labels indicating that the product can be allergenic.

Scheduling status

4-amino-3-nitrophenol is not specifically scheduled.

Scheduling history

4-amino-3-nitrophenol has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. In that submission it was noted that for this substance the industry has been applying the NITROPHENOLS entry in Schedule 6, which does not allow for exemptions of small quantities of nitrophenols. In general, the submission indicated support in aligning with the EU with up to 1% in ready-to-use preps and 1.5% for preps intended to be diluted prior to application.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that new Schedule 6, Appendix E and Appendix F entries be created for 4-amino-3-nitrophenol be created as follows:

Schedule 6—New Entry

PHENOL, 4-AMINO-3-NITRO **except**:

a) in non-oxidative hair dye preparations containing 1 per cent or less 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 sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

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

b) in oxidative hair dye preparations containing 1 per cent or less after mixing under oxidative conditions 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 sensitisation to certain individuals. 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 E—New Entry

PHENOL, 4-AMINO-3-NITRO

Part 1: Standard Statements: A

Appendix F—New Entry

PHENOL, 4-AMINO-3-NITRO

Part 1: Warning Statement: 28

The committee recommended an implementation date of 1 June 2016.

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 the substance.

The reasons for the recommendations comprised the following:

- The substance is used in hair dye products
- The substance is a strong skin sensitiser, has moderate to acute oral toxicity and therefore meets the criteria for inclusion in Schedule 6

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is accept the advice of the Committee and create a new Schedule 6, with appropriate exemption and cut-off, Appendix E and Appendix F entries.

Oxidative hair dyes of the aromatic diamine and aminophenolic classes have some common toxicological properties that warrant controls over scheduling. These features are primarily skin-eye irritancy and sensitization potential. These toxicological properties generally align with SPF criteria for listing in Schedule 6. Several of these dyes (e.g. phenylenediamines, toluenediamines; aminophenols) have already been listed in Schedule 6, but previous scheduling policies have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitization, and recommending testing for individual susceptibility before use. This approach is commonly called 'reverse scheduling'. Where there is potential mutagenicity, or the need to prevent uses for skin colouration (tattooing) or use to dye eyebrows or eyelashes, some of these substances have been listed in Schedule 10 to prevent such uses.

This is one of six oxidant hair dyes that were referred to the November 2015 meeting of the ACCS for advice to the delegate on scheduling. The key issues were whether their toxicological profiles sufficiently match the SPF criteria for inclusion in Schedule 6 and whether product exemptions based on 'reverse scheduling' could be applied, consistent with labelling provisions applied to other oxidative hair dyes. Given that some products containing oxidative hair dyes require mixing with an oxidant, such as hydrogen peroxide, before application to the hair; consideration was given to appropriate exemption cut-off concentrations that take account of the final concentration applied to the hair.

The delegate notes, and accepts, ACCS advice that 4-amino-3-nitrophenol should be listed in Schedule 6, with an exemption cut-off at 1%, provided products are labelled with the warning statements about potential skin sensitisation that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that warning statements relating to use for dyeing eyebrows and eyelashes are not needed, because the substance is not a strong irritant. The delegate also notes ACCS advice that 4-amino-3-nitrophenol is the name used in EU cosmetics regulations, is the preferred name for listing in Schedule 6, and that the existing Schedule 6 entry for NITROPHENOLS would not capture this substance, since it would not be considered to be a 'derivative'.

The proposed implementation date is **1 October 2016**.

A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

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

[6] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Schedule entry

Schedule 6—New Entry

4-AMINO-3-NITROPHENOL **except**:

a) in non-oxidative hair dye preparations and eyebrow/eyelash colouring products containing 1 per cent or less of 4-amino-3-nitrophenol 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 sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

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

b) in oxidative hair dye preparations and eyebrow/eyelash colouring products containing 1 per cent or less of 4-amino-3-nitrophenol after mixing under oxidative conditions 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 sensitisation to certain individuals. 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 E—New Entry

4-AMINO-3-NITROPHENOL

Part 1: Standard Statements: A

Appendix F—New Entry

4-AMINO-3-NITROPHENOL

Part 1: Warning Statement: 28

1.7 Amisulbrom

Scheduling proposal

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

· In August 2015, the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the approval of amisulbrom as a new active constituent and the registration of a product, containing amisulbrom, recommends that the delegate consider creating a new entry for amisulbrom in Schedule 6 of the SUSMP. No cut-off exemptions for amisulbrom were proposed by OCS.

Scheduling application

The reasons for the request were:

· OCS considers amisulbrom meets the Scheduling Policy Framework criteria for Schedule 6, based on results from a rabbit eye irritation study and carcinogenicity and mechanistic studies in rats and mice.

- The applicant did not nominate a Schedule for either amisulbrom or the product; in their APVMA application, the applicant indicated that they did not wish to nominate a Schedule proposal, but would defer to the outcome of the scheduling process.
- The applicant has been provided a copy of the OCS draft report and considered the OCS Scheduling recommendation. In their correspondence, the applicant does not dispute the OCS Schedule 6 recommendation for amisulbrom and the FAISD recommended for the product. However the applicant does not agree with OCS in relation to the classification of eye irritation according to the NOHSC Approved Criteria (NOHSC:1008, 2004) or GHS (5th Edition, 2013).
- In addition, although the applicant understands the logic for the R40 carcinogen category 3 classification for amisulbrom by OCS, the applicant has pointed out that the EU considered classification for carcinogenicity was not warranted as hepatocellular effects were seen at dose levels that exceeded the MTD.
- The applicant concludes that the liver effects seen at high doses in animal studies are of little relevance to realistic human exposure levels.
- In summary, the applicant, although agreeing with the OCS Scheduling recommendation is of the opinion that OCS has been overly conservative in their interpretation of both the eye irritation and carcinogenicity data.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS support listing in Schedule 6, based on the OCS recommendations?
- Does the ACCS agree with evaluation of the carcinogenic potential of amisulbrom, noting that the OCS evaluation does not believe that the evidence is sufficient to establish the proposed Mode of Action (MoA) suggesting a lack of human relevance for the proposed MoA?
- Is there a basis for establishing a cut-off to Schedule 5, or exempt, on the basis of the currently submitted evidence? Is there are need for a cut-off at this time, given that the product contains enough copper sulphate for it to be classified in Schedule 6?
- What name should be used for a listing in the Schedules – amisulbrom, or the IUPAC name 3-(3-bromo-6-fluoro-2-methylindole-1-ylsulfonyl)-N,N-dimethyl-1,2,4-triazole-1-sulfonamide?

Substance summary

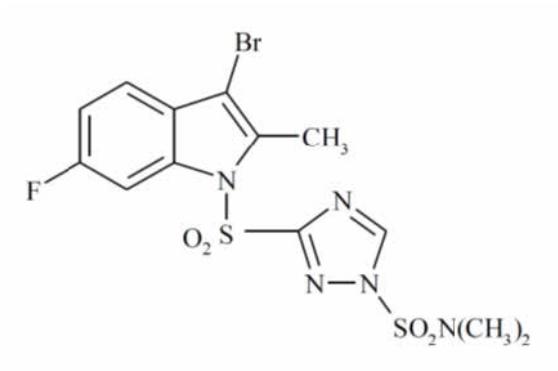


Figure 6: Chemical structure of amisulbrom

Acute toxicity

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

Toxicity	Species	Amisulbrom	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>5000 (no deaths)	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5000 (no deaths)	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h nose- only)	Rat	>2850 (no deaths)	N/A
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Rabbit	Moderate	Schedule 6
Skin sensitisation (GPMT)	Guinea Pig	Not sensitising	N/A

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

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

Toxicity	Species	The Product	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} >2000 (no deaths)	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} >2000	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h nose-only)	Rat	LC_{50} >2153 (no deaths)	N/A
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Rabbit	Slight irritant	N/A
Skin sensitisation (GPMT)	Guinea Pig	Not sensitising	N/A

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Repeat-dose toxicity

The systemic toxicity of amisulbrom in oral studies in rats, mice and dogs, consisted primarily of decreased body weight and body weight gain, food consumption and conversion efficiency and effects on the liver (e.g. serum liver enzyme changes, increased relative weights and hepatocyte hypertrophy),

kidney (increased relative weights and cortical tubular pigmentation) and adrenals (increased relative weights and cortical hypertrophy). No treatment related adverse effects were seen in a short-term dermal toxicity study in the rat, except a small decrease in weight gain in males at the highest dose (1000 mg/kg bw/d). No repeat dose inhalational toxicity studies were available for assessment. The toxicity profile for amisulbrom in repeat-dose toxicity studies (excluding carcinogenicity studies) in rats, mice and dogs indicates a low health hazard from repeated exposure and there was no indication of irreversible toxicity in these studies, except at doses above the MTD.

Mutagenicity

Potential genotoxicity of amisulbrom was assessed in a bacterial reverse mutation assay (Ames test; adequate S. typhimurium and E. coli strains; with and without metabolic activation [S9]), in vitro mutagenicity assay in mammalian cells (tk assay; mouse lymphoma cells; with and without metabolic activation), in vitro clastogenicity assay (human peripheral blood lymphocytes; with and without metabolic activation), in vivo mouse bone marrow micronucleus test (oral and intraperitoneal dosing), in vivo hepatic micronucleus test in rats (oral dosing), in vivo unscheduled DNA synthesis (UDS) assay (rats; oral dosing), in vivo hepatic comet assays in mice and rats and gastric mucosal cell comet assay in rats (oral dosing). The potential genotoxicity of the primary amisulbrom metabolite, IT-4 was assessed in a bacterial mutation assay ((Ames test; adequate S. typhimurium strains; with and without metabolic activation [S9]),) and a mouse micronucleus test. There was no evidence of a genotoxic potential associated with amisulbrom or IT-4.

Carcinogenicity

In long-term toxicity/carcinogenicity studies with rats (104 weeks) and mice (78 weeks), the target organs of toxicity were the liver and kidney. In the 1-year dog study, the target organs were the liver and adrenals.

Neoplastic findings in these studies were confined to rats and mice, as follows:

- an increased incidence of hepatocellular adenomas and carcinomas in male and female rats (i.e. ≥496 mg/kg bw/d in males, ≥697 mg/kg bw/d in females);
- an increased incidence of hepatocellular adenomas in male mice (≥98 mg/kg bw/d); and
- an increased incidence of squamous cell papillomas and carcinomas of the keratinised region of the forestomach in female rats and adenocarcinoma in males (i.e. ≥1008 mg/kg bw/d in males, ≥697 mg/kg bw/d in females).

Tumours of the forestomach were seen only at doses exceeding the MTD and appear to be related to chronic inflammatory changes caused by local irritation of the stomach mucosa. Histopathological lesions consistent with a local irritant effect in the gastrointestinal tract (epithelial hyperplasia, hyperkeratosis, ulceration and submucosal inflammation) were evident in animals at the same doses at which forestomach tumours were observed. Furthermore, consistent with a local inflammatory reaction in the gastrointestinal tract, sinus histiocytosis was seen in the mesenteric lymph nodes of females in the same dose groups. In addition, a rat forestomach gastric mucosa cell comet assay was negative. Given the high doses at which these effects occurred together with species differences in gastric fluid volumes and the fact that the anatomical target organ (the forestomach) is not present in humans, the forestomach tumours seen in rats are considered to have low relevance to humans.

Although liver tumours were only seen at high doses in rats, they were seen below the MTD in mice. The weight of evidence supports a non-genotoxic (epigenenetic) mechanism in rodents with a clear threshold for induction (i.e. no treatment-related induction of liver tumours occurred in male and female rats at 96 and 129 mg/kg bw/d, respectively, and mice at 11.6 mg/kg bw/d). Mechanistic studies, submitted by the applicant to elucidate the mechanism for liver tumours seen in both rats and mice, indicated a possible phenobarbital type mechanism for amisulbrom. However, although amisulbrom elicited similar DNA proliferative effects (RDS) and specific liver enzyme induction (mainly PROD activity) to phenobarbital, induction of CYP2B enzymes was not characterised and

CAR/PXR activation was not demonstrated. Overall, the OCS considers the mechanistic data are only suggestive of a possible phenobarbital type MOA for hepatic tumour formation in rodents and not sufficiently comprehensive or robust to eliminate the possibility of other modes of action leading to liver tumour formation. Therefore liver tumours seen in rodents are considered potentially relevant to humans.

Reproduction and developmental toxicity

Amisulbrom was not a reproductive toxicant (rats) or developmental toxicant (rats and rabbits). However, in a 2-generation dietary reproductive toxicity study in rats, although no effects were seen in F0 females, prolonged or irregular oestrous cycles, impaired fertility and ovarian atrophy were evident in F1 females. No effects on fertility were seen in males. Mechanistic studies (including anti-oestrogenic uterotrophic assay; anti-aromatase assay, reproductive hormone levels together with cross-fostering and food restriction studies) submitted by the applicant, provided evidence that impaired fertility in F1 females was likely a secondary response to reduced food intake and impaired body weight gain, associated with poor palatability of amisulbrom. Therefore impaired fertility seen in rodents is considered to have low relevance to humans.

Neurotoxicity

No neurotoxic effects (clinical signs, anatomical brain measurements, gross pathology, neurohistopathology or functional observation battery (FOB)) were observed in rats (both sexes) in an acute gavage study (single oral administration of amisulbrom up to 2000 mg/kg bw) or in a follow-up sub-chronic 13 week dietary study (doses up to 860 mg/kg bw/d (males) and 1132 mg/kg bw/d (females) in the same rat strain. The NOEL for general toxicity in the sub-chronic study was 23 mg/kg bw/d in males and 29 mg/kg bw/d in females, based on decreased body weight gain.

Observation in humans

No information was provided.

Public exposure

No information was provided.

International regulations

Amisulbrom has recently been considered for registration by the US EPA and EU (EFSA).

Scheduling status

Amisulbrom is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One public submission was received. In general, the submission supported a Schedule 5 entry and would accept a Sc `hedule 6 entry, as an entry in either schedule would not make any difference to end use product. The submission sought an expedient scheduling implementation date.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that a new Schedule 5 entry be created for amisulbrom as follows:

Schedule 5—New Entry

AMISULBROM

The committee recommended an implementation date of 1 June 2016.

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 the substance.

The reasons for the recommendations comprised the following:

- the active constituent for use in fungicide products
- the substance is a slight eye irritant
- the substance meets the criteria for inclusion 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*;
- Scheduling factors[7];
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, advice from the ACCS that amisulbrom be listed in Schedule 5. The delegate agrees that the overall toxicological profile of amisulbrom is consistent with SPF criteria for listing in Schedule 5 and that the eye irritancy potential is more appropriately categorised as slight, rather than moderate. The delegate notes that the ACCS considers the evidence for the MoA producing liver tumours in rats and mice is sufficient to discount the relevance of these findings for humans.

Despite the apparent low toxicity profile of the product submitted for evaluation, an exemption cut-off for amisulbrom is not proposed at this time. The submitted product would require Schedule 6 controls since it includes copper sulphate at a concentration exceeding the Schedule 5 range of 5 – 15% that would qualify for the exemption from the Schedule 6 entry for copper sulphate.

The proposed implementation date is **1 June 2016**.

The earliest practicable implementation of the scheduling decision will facilitate approval of the substance by the APVMA.

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

[7] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Schedule entry

Schedule 5—New Entry

AMISULBROM

1.8 C.I. Direct Orange 1

Scheduling proposal

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

- In August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) Programme, referred a proposal to amend the entry for BENZIDINE-BASED AZO DYES in Schedule 7 to include C.I. Direct Orange 1 in the Poison Standard by the delegate.

Scheduling application

The reasons for the request were:

- That whilst the data for the actual chemical are limited, C.I. Direct Orange 1 has been identified as a benzidine-based azo dye.
- Benzidine based-dyes have been shown to be metabolised to benzidine, a known human carcinogen.
- In June 2013, NICNAS completed an assessment of a number of azo dyes which may break down to produce the potent carcinogen, benzidine. The chemicals were recommended for scheduling to prohibit their sale, supply and use in consumer products (NICNAS). The scheduling delegate decided to list the chemicals in Schedule 7 of the Poisons Standard (effective as of 1 June 2014). In the absence of similar regulatory controls, this chemical could also pose an unreasonable risk to the public.
- In November 2014, a similar proposal for scheduling C. I. Acid Black 29, another benzidine-based dye not included in the original NICNAS assessment, was agreed by ACCS.
- The scheduling of this chemical would be consistent with scheduling decisions with other benzidine-based dyes.
- The proposal is to add C.I. Direct Orange 1 to the existing BENZIDINE-BASED AZO DYES entry in Schedule 7. The SPF recommends that proposals to list in S7 be referred to the ACCS, and this will also offer industry an opportunity to provide comment on potential regulatory impacts.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of C.I .Direct Orange 1 is consistent with other benzidine-based azo dyes, and therefore warrants addition to that entry? Adding C.I. Direct Orange 1 to the current list of substances covered by this generic entry would be consistent with the way that listing of C.I. Acid Black was recommended at the November 2014 ACCS meeting.
- Should the entry list both the common name (C.I Direct Orange 1) and the CAS number? As a secondary issue, does the ACCS support a recommendation to the TGA that the current formatting of the BENZIDINE-BASED AZO DYES entry in Poisons Standard July 2015 be addressed, so that CAS numbers are appropriately aligned with the substances to which they refer, and missing CAS numbers are re-inserted?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) human health Tier II assessment report for C.I. Direct Orange 1.

The critical concern for this chemical and the focus of this assessment relates to the potential carcinogenic effects following exposure. Data are available for four benzidine-based dyes; Direct Red 28 (CAS No. 573-58-0), Direct Blue 6 (CAS No. 2602-46-2), Direct Black 38 (CAS No. 1937-37-7) and Direct Brown 95 (CAS No. 16071-86-6). Based on the common metabolite, benzidine, the data are considered representative for C.I. Direct Orange 1. These data can be found on the NICNAS website.

Toxicokinetics

Metabolism of benzidine-based dyes to free benzidine and its metabolites have been observed in both humans and animals.

In vivo, azo reduction of benzidine-based substances, liberating free benzidine, occurs by an enzyme-mediated reaction. The intestinal microflora have been shown to be particularly active in azo dye reduction, but hepatic enzymes can also catalyse the reductive cleavage.

Bacteria on the skin have also been shown to possess azoreductase activity.

Genotoxicity

No data are available for the chemical. However, a dose-related increase in the number of circulating peripheral lymphocytes displaying chromosomal aberrations was observed in workers exposed to benzidine and benzidine-based dyes (Direct Black 38 and Direct Blue 6). The highest frequencies of aberrant lymphocytes were associated with the highest airborne dust concentrations of benzidine (0.42–0.86 mg/m^3) or benzidine-based dyes (7.8–32.3 mg/m^3), and with the highest mean levels of benzidine found in the urine (1.8–2.3 µg/L). The frequency of polyploid lymphocytes was also elevated in workers when compared with controls (ATSDR, 2001; IARC 2010 (referenced in C.I. Direct Orange 1 IMAP report)).

Carcinogenicity

No data are available for the chemical. However, the related chemicals Direct Red 28, Direct Black 38, Direct Blue 6 and Direct Brown 95 are currently classified as hazardous as Category 2 carcinogens with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). Several other benzidine-based dyes are recommended for classification for carcinogenicity (refer to the IMAP report).

Three benzidine-based dyes (Direct Black 38, Direct Blue 6 and Direct Brown 95) have been tested for carcinogenicity in animals. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the carcinogenicity of all dyes metabolised to benzidine on the basis of these studies. Observed effects included increased incidence of hepatocellular carcinomas and liver neoplastic nodules with all three dyes, and mammary gland cancers with Direct Black 38. A slight increase in transitional cell carcinoma of the urinary bladder was observed in an implantation study with Direct Blue 6. Hepatocellular carcinomas and liver neoplastic nodules were observed for all three dyes, despite a relatively short exposure period of 13 weeks (NTP, 2011; IARC, 2012; Government of Canada, 2013 (referenced in C.I. Direct Orange 1 IMAP report)).

The evidence of bladder cancer for workers exposed to benzidine-based dyes was not consistent across studies. There were limitations in the studies, including coexposure to known carcinogens in humans. Despite this, IARC has classified dyes metabolised to benzidine as carcinogenic to humans (Group 1) and the US National Toxicology Program has also classified dyes metabolised to benzidine as 'known to be human carcinogens'. The classification was based on findings that:

· benzidine is known to be a human carcinogen;

- the metabolism of benzidine-based dyes results in the release of free benzidine and the induction of chromosomal aberration in humans; and
- benzidine exposure from exposure to benzidine-based dyes is equivalent to exposure to equimolar doses of benzidine.

Reproductive and developmental toxicity

No data are available for the chemical. However, the related chemicals Direct Red 28, Direct Black 38 and Direct Blue 6 are classified as hazardous—Category 3 substances toxic to reproduction—with the risk phrase 'Possible risk of harm to the unborn child' (T; R63) in HSIS (Safe Work Australia). Several other benzidine-based dyes are recommended for classification for developmental toxicity (see the IMAP report).

Public exposure

Whilst the use of benzidine-based dyes is being phased out in some countries, use of the chemical as a dye has been reported internationally. The introduction of this chemical for home use cannot be excluded.

International regulations

Cosmetics

No known restrictions have been identified for the chemical. However, the related benzidine-based dyes, Direct Red 28 (CAS No. 573-58-0), Direct Black 38 (CAS No. 1937-37-7), Direct Blue 6 (CAS No. 2602-46-2) and Direct Brown 95 (CAS No. 16071-86-6) are listed on the following (Galleria Chemica):

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products - Annex II - List of Substances Prohibited in Cosmetic Products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

Other

Access to benzidine based dyes for home use is no longer permitted in the USA (NTP, 2011).

The chemical is restricted by Annex XVII to REACH Regulation as follows:

1. Azo dyes which, by reductive cleavage of one or more azo groups, may release one or more of the aromatic amines listed in Appendix 8, in detectable concentrations, i.e. above 30 ppm in the finished articles or in the dyed parts thereof, according to the testing methods listed in Appendix 10, shall not be used in textile and leather articles which may come into direct and prolonged contact with the human skin or oral cavity, such as:

- clothing, bedding, towels, hairpieces, wigs, hats, nappies and other sanitary items, sleeping bags;
- footwear, gloves, wristwatch straps, handbags, purses/wallets, briefcases, chair covers, purses worn round the neck;
- textile or leather toys and toys which include textile or leather garments; and
- yarn and fabrics intended for use by the final consumer.

2. Furthermore, the textile and leather articles referred to in paragraph 1 above shall not be placed on the market unless they conform to the requirements set out in that paragraph.'

Scheduling status

CI. Direct Orange 1 is not specifically scheduled.

Scheduling history

CI. Direct Orange 1 has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. There was no objection to the proposal.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that the following amendments (highlighted in red) be made to the Schedule 7 entry for BENZIDINE-BASED AZO DYES to include C.I. Direct Orange 1 (CAS No. 545779-28-1) and insert any missing CAS numbers as follows:

Schedule 7—Amend Entry

BENZIDINE-BASED AZO DYES

- 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)
- C.I. Direct Orange 1 (CAS No. 54579-28-1)
- 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)

The committee recommended an implementation date of 1 June 2016.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendations comprised the following:

- To be consistent with previous decisions made on azo-based dyes
- Azo-dyes are considered to be carcinogenic in animal data and in-vitro testing

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[8];
- Other relevant information.

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 Direct Orange 1 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.

[8] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Only the dye name/number and CAS number are to be included in the listing, without the chemical name as for other listings, since it appears that C.I Direct Orange 1 may be a mixture of three different substances. In addition, as an editorial amendment, the missing CAS number for C.I. Acid Black 29 is to be included.

The proposed implementation date is **1 June 2016**.

This is the earliest practicable date on which this schedule can be implemented in the Poisons standard.

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

Schedule entry

Schedule 7—Amend Entry

BENZIDINE-BASED AZO DYES

- 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)
- C.I. Direct Orange 1 (CAS No. 54579-28-1)
- 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)

1.9 Dyes that could release selected carcinogenic amines (not listed on AICS)

Scheduling proposal

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

- To create a new entry for various dyes that could release selected carcinogenic amines (not listed on AICS) and/or the aromatic amine precursors in Schedule 7 or Appendix C.

Scheduling application

The reasons for the request were:

- Although the data for the actual dyes are limited, the chemicals are all considered to have the potential to be metabolised to the following carcinogenic and/or genotoxic aromatic amines through reductive cleavage of the azo linkage:
  - 2-naphthylamine (CAS No. 91-59-8);
  - 2,4,5-trimethylaniline (CAS No. 137-17-7); and
  - 6-methoxy-m-toluidine (*p*-cresidine) (CAS No. 120-71-8).
- Although the commercial production of Ponceau 3R and dyes based on 2-naphthylamine is restricted in some countries, this does not appear to be the case for dyes based on p-cresidine. In addition, commercial production in other countries such as India and China is not known.
- The scheduling of these dyes would be consistent with scheduling decisions on other azo dyes that have the potential to be metabolised to known carcinogens.
- Trace levels of the aromatic amines used in dye production could be technologically inevitable.
- The delegate's reason for referring this scheduling proposal to the ACCS is that, in accordance with section 4.2 of the Scheduling Policy Framework (SPF), advice is required to be obtained from an expert advisory committee for all proposals to list in Schedule 7, and this will also offer industry an opportunity to provide comment on potential regulatory impacts.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Noting the scheduling approaches to the restrictions on benzidine-based azo dyes and benzidine congener (3,3'-disubstituted) based azo dyes from the 2013 and 2014 November ACCS meetings, and for other azo dyes that can be de-azotised to carcinogenic aromatic amines at the August 2015

ACCS meeting, does the ACCS support creation of an additional listing for five azo dyes listed in the NICNAS IMAP report?

- Should this listing be in Schedule 7 or 10? Should the listing(s) be for the named substances, along with their CAS numbers, or should they be added to the generic entry developed at the August 2015 ACCS meeting? If the substances are named individually, should they be listed as the sodium salts (as in the IMAP report), or named such as to capture all salts?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) human health Tier II assessment report for Dyes that could release selected carcinogenic amines (not listed on AICS).

The critical concern for this group of chemicals and the focus of this assessment relates to the potential carcinogenic effects following exposure. The toxicological data for the chemicals in this group are limited. However, these azo compounds could undergo reductive cleavage of their azo bonds, releasing the following aromatic amines that have known carcinogenic potential: 2-naphthylamine; 2,4,5-trimethylaniline; and p-cresidine. These aromatic amines, are classified carcinogens in Australia. In addition, 2-naphthylamine (cleavage product of CAS No. 85186-64-7 and CAS No. 85186-66-9), is identified as a prohibited carcinogen (Table 10.1, Schedule 10) in Workplace Health and Safety legislation (WHS Regulations, 2011). Whilst these aromatic amines are not listed on the AICS, they are reported to be used overseas. Therefore, these chemicals could potentially be present as impurities in products imported into Australia.

This group of dyes represents the fourth such submission arising from IMAP. The previous three, for dyes based on benzidine, dyes based on benzidine congeners, and dyes based on other carcinogenic amines listed on AICS, have resulted in ACCS recommendations and/or Delegate's decisions for Schedule 7 listing. The current group completes the set of dyes based on "EU 22" amines forwarded for scheduling. The critical fact that separates this group from the previously (August 2015) considered group is that, as the amines are not on AICS, there are no IMAP reports on the amines available for reference, and so consideration of the carcinogenicity of the amines is contained within the assessment of the dyes (see IMAP report).

Genotoxicity

Based on the limited data available, it is not possible to draw a definite conclusion regarding the genotoxicity of the chemicals in this group. Although available data are neither sufficient nor adequately comprehensive for classification, a genotoxic mode of action cannot be ruled out. Studies on the aromatic amines that are potential cleavage products of the chemicals in this group (2-naphthylamine, 2,4,5-trimethylaniline and p-cresidine) demonstrated genotoxicity/mutagenicity in a number of in vitro and in vivo assays (see IMAP report for more details).

Carcinogenicity

Limited data are available for the carcinogenic potential of the chemicals in this group.

Ponceau 3R is reported to produce tumours in rat livers and mouse urinary bladders. Long-term oral exposure (feeding studies) to Ponceau 3R of up to two years with 0.5–5 % doses in the diet) produced liver tumours in rats (Wistar, Osborne–Mendel, Bethesda Black). These include hepatomas, hepatic adenomas, bile duct adenoma, and adenomatous or nodular hyperplasia (Grice et al., 1961; Mannell, 1964; Aiso et al., 1966; IARC, 1975). The authors suggested that the component compounds present in the chemical, such as 2,4,5-trimethylaniline, contributed to the observed carcinogenic activity of Ponceau 3R (Mannell, 1964). In mice, Ponceau 3R produced bladder tumours on implantation in the urinary bladder (IARC, 1975 (referenced in the IMAP report)).

The International Agency for Research on Cancer (IARC) has classified Ponceau 3R as 'Possibly carcinogenic to humans' (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal testing (IARC, 1987 (referenced in the IMAP report)).

Although data are not available for the other chemicals in this group, the aromatic amines that could be released following the azo bond reductive cleavage of these chemicals are known carcinogens.

The aromatic amine, 2-naphthylamine, is classified as hazardous—Category 1 carcinogenic substance—with the risk phrase 'May cause cancer by inhalation' (T; R45) in the (HSIS) (Safe Work Australia).

The IARC has classified 2-naphthylamine as 'known to be a human carcinogen based on the sufficient evidence of carcinogenicity from studies in humans'. A number of studies reported a significant increase in human urinary bladder tumours caused by occupational exposure. Experimentally, urinary bladder tumours were also seen in several species of laboratory animals (rat, hamster, dog and monkey) following repeated exposures to 2-napthylamine via a number of routes including oral, dermal, subcutaneous, intraperitoneal, intravesicular implantation and bladder-instillation (IARC, 2010 (referenced in the IMAP report)). Liver and lung tumours were also observed in mice.

The aromatic amines, p-cresidine and 2,4,5-trimethylaniline are classified as Category 2 carcinogenic substances—with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). These aromatic amines are considered as 'reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals' (IARC, 1982; NTP, 2011 (referenced in the IMAP report)).

Long-term oral exposure to p-cresidine produced malignant and benign tumours in the urinary bladder and liver of rats and mice, and nasal cancer in rats (NTP, 2011). Chronic exposure of rats and mice to 2,4,5-trimethylaniline caused lung and liver tumours (NCI, 1979; NTP; Wiley VCH (referenced in the IMAP report)).

Metabolic activation of aromatic amines to produce nitrenium ion metabolites, which cause DNA adduct formation and induction of DNA damaging effects, has been postulated to be the likely mechanism of action for their carcinogenicity (SCCNFP, 2002 (referenced in the IMAP report)). The IARC concluded that 'there is strong mechanistic evidence that the carcinogenicity of 2-napthylamine operates by a genotoxic mechanism of action' (IARC, 2010 (referenced in the IMAP report)).

Public exposure

Although the commercial production of Ponceau 3R and dyes based on 2-naphthylamine is restricted in some countries, this does not appear to be the case for dyes based on p-cresidine and 2,4,5-trimethylaniline. In addition, commercial production in other countries such as India and China is not known. Therefore the introduction of these dyes for home use cannot be excluded.

International regulations

Cosmetic

The chemicals are restricted by the EU Annex XVII to EU Regulation as follows:

1. Azo dyes which, by reductive cleavage of one or more azo groups, may release one or more of the aromatic amines listed in Appendix 8, in detectable concentrations, i.e. above 30 ppm in the finished articles or in the dyed parts thereof, according to the testing methods listed in Appendix 10, shall not be used in textile and leather articles which may come into direct and prolonged contact with the human skin or oral cavity, such as:

· clothing, bedding, towels, hairpieces, wigs, hats, nappies and other sanitary items, sleeping bags;

· footwear, gloves, wristwatch straps, handbags, purses/wallets, briefcases, chair covers, purses worn round the neck;

· textile or leather toys and toys which include textile or leather garments; and

· yarn and fabrics intended for use by the final consumer.

2. Furthermore, the textile and leather articles referred to in paragraph 1 above shall not be placed on the market unless they conform to the requirements set out in that paragraph'.

Appendix 8 is the list of the "EU 22" aromatic amines.

Scheduling status

None of the dyes listed above are not specifically scheduled.

Scheduling history

None of the dyes listed above have been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. No general objections to proposal, however they note that changing labelling may require a period of transition.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that the group Schedule 7 entry for AZO DYES that are derivatives by diazotisation of any of the following substances be amended to include the additional following highlighted in red:

Schedule 7—Amend Entry

AZO DYES that are derivatives by diazotisation of any of the following substances:

- o-anisidine (CAS No. 90-04-0)
- o-toluidine (CAS No. 95-53-4)
- p-aminoazobenzene (CAS No. 60-09-3)
- o-aminoazotoluene (CAS No. 97-56-3)
- 2,4-toluenediamine (CAS No. 95-80-7)
- 5-nitro-o-toluidine (CAS No. 99-55-8)
- p-chloroaniline (CAS No. 106-47-8)
- 2-naphthylamine (CAS No. 91-59-8)
- 2,4,5-trimethylaniline (CAS No. 137-17-7)
- 6-methoxy-m-toluidine (p-cresidine) (CAS No. 120-71-8)

The committee recommended an implementation date of 1 June 2016.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendations comprised the following:

- To be consistent with previous decisions made on azo-based dyes
- Azo-dyes are considered to be carcinogenic in animal data and in-vitro testing

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The NICNAS IMAP program has previously referred for possible listing in Schedule 7, a number of azo dyes based on the known human carcinogen benzidine, as well as some dyes based on benzidine congeners and those that can be reduced by azo reductases to carcinogenic amine components. Following referral to the August 2015 meeting of the ACCS, the delegate agreed to Schedule 7 listing for azo dyes that can be reduced by azoreductases to yield 8 specific carcinogenic aromatic amines: o-anisidine (CAS No. 90-04-0); o-toluidine (CAS No. 95-53-4); p-aminoazobenzene (CAS No. 60-09-3); o-aminoazotoluene (CAS No. 97-56-3); 2,4-toluenediamine (CAS No. 95-80-7); 5-nitro-o-toluidine (CAS No. 99-55-8);p-chloroaniline (CAS No. 106-47-8);and 4-chloro-o-toluidine (CAS No. 95-69-2). The current proposal seeks to extend the list of carcinogenic amines is this generic entry, in order to capture some additional potentially carcinogenic amines, specifically 2-naphthylamine (CAS No. 91-59-8); 2,4,5-trimethylaniline (CAS No. 137-17-7); and 6-methoxy-m-toluidine(p-cresidine) (CAS No. 120-71-8).

The delegate accepts ACCS advice that the dyes referred in the current submission should also be controlled for use in consumer products by listing in Schedule 7, and agrees that adding them to the current generic listing for AZO DYES *that are derivatives by diazotisation of any of the following substances:* **...** would achieve this objective. The delegate notes a point raised in a public submission that some of the listed aromatic amines may be present as manufacturing impurities in the relevant azo dyes. However, since the objective is to control the parent dyes themselves, and the resultant aromatic amines are not specifically listed as individual substances in Schedule 7, this should not be a problem.

The proposed implementation date is **1 June 2016**.

The earliest practicable implementation date is warranted since the objective is to remove any such products from the Australian market on safety grounds.

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

Schedule entry

Schedule 7—Amend Entry

AZO DYES that are derivatives by diazotisation of any of the following substances:

- o-anisidine (CAS No. 90-04-0)
- o-toluidine (CAS No. 95-53-4)

[9] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

- p-aminoazobenzene (CAS No. 60-09-3)
- o-aminoazotoluene (CAS No. 97-56-3)
- 2,4-toluenediamine (CAS No. 95-80-7)
- 5-nitro-o-toluidine (CAS No. 99-55-8)
- p-chloroaniline (CAS No. 106-47-8)
- 2-naphthylamine (CAS No. 91-59-8)
- 2,4,5-trimethylaniline (CAS No. 137-17-7)
- 6-methoxy-m-toluidine (p-cresidine) (CAS No. 120-71-8)

1.10 Isethionate

Scheduling proposal

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

- To include a new Schedule 5 entry for isethionate (2-hydroxyethanesulfonic acid).

Scheduling application

In August 2014, the Applicant, as part of an application to the Australian Pesticides and Veterinary Medicines Authority (APVMA), requested that the delegate consider not including isethionate in a schedule entry. The OCS evaluated the information provided by the applicant and advised the applicant (in the draft human health risk assessment report of August 2015) that a Schedule 5 entry is appropriate for isethionate.

The applicant responded to the August 2015 OCS draft human health risk assessment report indicating that they have no objections to OCS's scheduling proposal.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- The name 'isethionate' seems inappropriate for listing. The CAS No. 57267-78-4 specifically refers to the ammonium salt of 2-hydroxyethanesulfonic acid. Should an entry in the Schedules refer to that ammonium salt under that name, or should the entry specify 2-hydroxyethansulfonic acid, therefore picking up all salts?
- The product under consideration is a mixture of the ammonium, monoethanolamine, diethanolamine, triethanolamine and tetraethanolamine salts (887g/l in all). The toxicity tests were all done with this mixture. There are current SUSMP entries for mono-, di- and tri-ethanolamines in Schedules 6 (>20%) and 5 (5-20%), with only preparations <5% exempt. All these entries exempt salts and derivatives, so there may not be an issue that the proposed product would be captured by the current ethanolamine entries. Does the ACCS confirm that the proposed listing in S5 for this product will not conflict with current ethanolamine entries?
- Are there any non-AgVet products or uses of 2-hydroxyethansulfonic acid (isethionate) or its salts that might be inadvertently captured by the proposed entry?

Substance summary

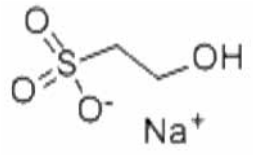


Figure 7. Chemicals structure of isethionate (sodium salt)

Acute toxicity

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

Toxicity	Species	Isethionate	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	Low (LD_{50} >2000 mg/kg bw)	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	Low (LD_{50} >2000 g/kg bw)	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	Low (LC_{50} >6295 mg/m^3)	Schedule 5
Skin irritation	Rabbit	Non-irritant	-
Eye irritation	Rabbit	Slight	Schedule 5
Skin sensitisation	Guinea pig	Non-sensitiser	-

Repeat-dose toxicity

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, Wistar Hannover rats (12/sex/dose) were orally administered the test substance via gavage at 0, 250, 500 or 1000 mg/kg bw isethionate. Male rats received the test substance for 28 days and female rats received the test substance for 54 days (including pre-mating, mating and through gestation and lactation). A satellite group of animals (5/sex) were administered 0 and 1000 mg/kg bw/d of the substance to assess reversibility of findings. Deionised water was used as a vehicle.

There were no mortalities, treatment related clinical findings including neurobehavioral changes in any of the treatment groups. Slight changes in body weight and body weight gain were observed. However, these changes in bodyweight and bodyweight gain were small in magnitude and there was no time or dose response relationship, and were not considered to be treatment related. There was no adverse, treatment related effect on food consumption in any of the treatment groups.

Changes in haematology parameters included decreased mean red blood cell count, haemoglobin, haematocrit and platelets in the mid and highest doses, attaining statistical significance in high dose males (red blood cell count, haemoglobin and haematocrit). Moreover, animals exposed to 500 and 1000 mg/kg bw/d showed changes in clinical chemistry parameters, however there was no clear, consistent, and statistically significant, dose related adverse effects observed at any dose and therefore were not considered to be treatment related.

Both male and female rats exposed to 500 mg/kg bw/d showed increased kidney weights. Increased adrenal weights were seen in males exposed to 500 and 1000 mg/kg bw/d. Low incidence microscopic

findings were observed in high dose males including pelvis dilatation and mild congestion in the kidney, mild bilateral tubular degeneration of the testis and mild bilateral tubular degeneration of the epididymis.

Low incidence microscopic findings were observed in high dose females including mild diffuse vacuolisation and isolated hepatocellular hyperthrophy of the liver, slight unilateral pelvis dilatation and slight congestion in the kidney, slight unilateral kidney pelvis dilatation and slight bilateral pelvis dilatation of the kidney.

However, a comprehensive histopathological examination of tissues was not conducted as only the high dose and control animals were examined microscopically. Therefore, the toxicological significance of these findings is unknown in the absence of microscopic examination in the mid-dose groups.

Genotoxicity

The genotoxic potential of the compound was tested in an Ames test using four strains of *S. typhimurium* and a strain of *E. coli* which gave negative results with and without metabolic activation.

Carcinogenicity

The applicant did not provide carcinogenicity studies.

Reproduction and developmental toxicity

A separate reproduction or developmental toxicity study has not been provided by the applicant. The repeat dose toxicity study (discussed under Repeat-Dose Toxicity) provided by the applicant contained a reproductive/developmental toxicity screening test for isethionate.

In the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, rats (12/sex/dose) were orally administered the test substance via gavage at 0, 250, 500 and 1000 mg/kg bw/d. Male rats received the test substance for 28 days and female rats were received the test substance for 54 days (including pre-mating, mating and through gestation and lactation). A satellite group of animals (5/sex) were administered 0 and 1000 mg/kg bw/d of the substance to assess reversibility of findings.

Changes in a number of reproductive effects, including increased pre-implantation loss (17.9% increase), decreased fertility index (22.3% decrease) and increased gestation index (12.5% increase) were seen in the high dose treatment group compared with controls. These were not statistically significant and there was no clear dose response relationship to the findings.

Evaluation of pups and litter showed that on day zero, one pup out of 69 and on day four, one pup out of 68 from the control group died. One pup out of 90 treated with 250 mg/kg bw/d and six pups out of 75 treated with 500 mg/kg bw/d of the test substance were found dead on day four, however there were no dead pups in the high dose group. Therefore, in the absence of a dose response relationship and the low magnitude of pup deaths, the finding was not considered to be treatment related. The mean body weight of pups on days zero and four postnatal was similar in all groups.

Observation in humans

No information was provided.

Public exposure

No information was provided.

International regulations

No information was provided.

Scheduling status

Isethionate is not specifically listed in the SUSMP.

Scheduling history

Isethionate has not been considered for scheduling previously.

Pre-meeting public submissions

Two public submissions were received. The first submission questions the wording of the entry: isethionate (2-hydroxyethanesulfonic acid) noting that according to Part 1, Section 2 of the Poisons Standard, all salts and derivatives are included in entries, unless specified. Isethionate and its salts are used in some cosmetic products and scheduling will impact those existing products. The US Cosmetic Ingredient Review (CIR) deemed isethionate as a safe cosmetic ingredient, when formulated to be non-irritating. The submission seeks for isethionate to remain unscheduled or at least to have a lengthy implementation date applied.

The second submission states isethionate salts are used as alternatives to lauryl sulfates in cosmetics. It refers to the US CIR on isethionate salts that concluded these to be safe for use in cosmetics when formulated to be non-irritating. The submission suggests surfactants do not require scheduling as the risks are known to consumers and due to no international restrictions being in place. They note, however, that a precedent has been set, with ammonium cocoyl isethionate appearing in Schedule 6. Therefore they ask if scheduling is decided upon that a low cut-off (currently used at up to 25%) in rinse-off cosmetics be put in place.

The public submission is available at the TGA website.

ACCS advice to the delegate

The committee recommended that 2-hydroxyethansulfonic acid and its salts does not require a schedule listing but that the Delegate consider listing the substance in Appendix B for reasons of Part 2, Areas of Use.

The reasons for the recommendations comprised the following:

- The committee noted that the data for the substance was lacking, and what data there is points to a marginal toxicological profile. The Committee agreed that there is no real requirement to schedule and an entry in Schedule 5 would not have any real regulatory impact.

The committee also proposed a new reason in Appendix B, Part 2, Area of Use be created with wording to the effect of *adjuvants in agricultural products*.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

- Scheduling factors[10];
- Other relevant information.

Delegate's interim decision

The specific application for scheduling under consideration relates to the use of mixed salts of 'isethionate' as an adjuvant in agricultural herbicide tank mixes. The delegate notes, and accepts, ACCS advice that this substance does not require listing in the Schedules because of its low toxicity and use pattern. Listing in Appendix B for this specific agricultural use avoids any scheduling impacts associated with the use of isethionate salts in cosmetics and other domestic products, as flagged in the industry submissions.

The proposed addition to the SUSMP is **1 June 2016**.

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

Schedule entry

Appendix B—New Entry

ISETHIONATE, as mixed ammonium and ethanolamine salts of 2-hydroxyethanesulfonic acid

Part 1 – Reasons for Entry

a) low toxicity; and

b) use pattern restricts hazard

Part 2 - Area of Use

1.11 Adjuvant in agricultural products

1.11 1-(1,1-Dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene (musk ambrette)

Scheduling proposal

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

- To create a new entry for 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene- (musk ambrette) in Schedule 10 to prohibit the use in cosmetic and domestic products.

Scheduling application

In August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the proposal to be considered by the delegate. The reasons for the request are:

- the chemical has reported cosmetic and domestic uses internationally. Use in Australia is unknown;
- the chemical is neurotoxic and a reproductive toxicant at low doses;
- the chemical is prohibited in cosmetics overseas; and

[10] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

- the chemical is prohibited under the international fragrance association (IFRA) Standard.

Musk ambrette is a strong neurological and testicular toxicant at low exposures and also has a potential for photosensitisation. The chemical is toxic via dermal contact and hence, there is a concern for the use in cosmetic and domestic products. The environmental assessment also concluded that the chemical is expected to be persistent in the environment.

The European (EU) and Association of Southeast Asian Nations (ASEAN) countries as well as New Zealand have prohibited the use of musk ambrette in cosmetic products. While musk ambrette is generally considered to be phased out the chemical was reported to be used in Denmark in 2012.

Based on the scheduling factors the appropriate parent Schedule is 7 or 10. However, considering that the use of the chemical as a fragrance is prohibited overseas, and other uses are not likely to occur in Australia, Schedule 10 is probably appropriate in this case.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- The ACCS has previously considered a number of fragrance chemicals for scheduling, where sensitisation potential has often been the adverse health effect on which scheduling has been recommended. The ACCS has generally recommended that scheduling is not an appropriate process to regulate those chemicals likely to be present at such low concentrations that there should be no public health hazard.
- The NICNAS IMAP notes the photosensitisation potential for musk ambrette (not direct skin sensitisation), but it also draws attention to the potential for neurotoxicity and reproductive toxicity. Neurotoxicity was dose-related from 40-240 mg/kg/d in a dermal rat study. The reproductive toxicity (testicular atrophy) was demonstrated in studies in rats at low oral doses (2.5 mg/kg/d) but only at somewhat higher dermal doses (240 mg/kg/d). Is the evidence for potential photoallergenicity, neurotoxicity and reproductive toxicity sufficient to warrant a new entry for musk ambrette in Schedule 10?
- Should such a Schedule 10 entry be specific to prevent use in cosmetics only, or should this restrictive schedule relate to its use as a fragrance ingredient in domestic cleaning products?

Substance summary

Please refer to the NICNAS IMAP Human Health Tier II assessment report for benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro-. This report is publicly available on the NICNAS website.

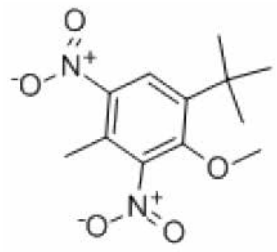


Figure 8. Chemicals structure of musk ambrette

Acute toxicity

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

Toxicity	Species	Musk ambrette	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	339	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	>2000	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	N/A
Skin irritation	Rabbit	Not expected to be an irritant	N/A
Eye irritation	Rabbit	Not expected to be an irritant	N/A
Skin sensitisation	N/A	No data	N/A

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Photoallergy studies

In a photosensitivity study in guinea pigs with limited data, musk ambrette was positive for photosensitivity after application to abraded skin, or under occlusive conditions.

In a local lymph node assay, musk ambrette did not induce a positive photo-allergic response. No further details were provided.

Human data also indicate photosensitisation potential of musk ambrette.

Repeat-dose toxicity

Based on the data available from the NICNAS IMAP report, the chemical is neurotoxic via oral and dermal exposure.

Oral

In a repeated dose oral toxicity study in rats (strain not provided), 0.5–4 mg/kg bw/day of musk ambrette was fed to rats in the diet. Treatment-related clinical signs included growth retardation and progressive paralysis of hind limbs at 1.5 mg/kg bw/day. Observations at 16–40 weeks showed complete hind limb paralysis in the animals at the high dose. Depressed erythrocyte counts and haemoglobin values in female rats were observed at doses of ≥1.5 mg/kg bw/day of the chemical. Jaundice at all dose levels was observed. Neuropathological changes reported were primary demyelination and distal axonal degeneration.

In a 12-week repeated dose oral toxicity study, young Sprague Dawley (SD) male and female rats were orally administered musk ambrette at 1500 ppm (approximately 75 mg/kg bw/day) of the chemical. Clinical and haematological examinations were conducted after six and 12 weeks. Hind limb weakness was observed in 20/40 treated animals.

Dermal

In a 12-week repeated dose dermal toxicity study, young SD rats of both sexes were treated by dermal application of a patch with musk ambrette solution in phenyl ethyl alcohol (PEA) at concentrations of 10, 40, 80, or 240 mg/kg bw/day. Clinical and haematological examinations were conducted after six and 12 weeks. No adverse skin reactions to the patch were seen in any of the treatment groups. Hind limb weakness was observed in 1/30 animals treated at 40 mg/kg bw/day, 15/30 animals treated at 80 mg/kg bw/day and all animals treated at 240 mg/kg bw/day. All animals treated with 240 mg/kg bw/day showed severe neuropathological changes in the central and peripheral nervous system. The severity of the changes was dose-related.

Genotoxicity

The limited data available from several equivocal genotoxicity studies are insufficient for the chemical to be considered genotoxic.

Carcinogenicity

No data are available on the chemical. The data for the structurally related chemical, musk xylene suggest that the mode of action for induction of liver tumours in mice is similar to that for phenobarbital. The relevance of this mode of action to humans has been questioned.

Reproduction and developmental toxicity

The chemical is considered to be a severe reproductive toxicant at low doses.

In a repeated dose oral toxicity study in rats (strain not provided), 0.5–4 mg/kg bw/day of musk ambrette was fed to rats in the diet. Histopathological investigation showed treatment-related testicular atrophy at 2.5 mg/kg bw/day.

In a 12-week repeated dose dermal toxicity study, young SD rats of both sexes were treated by dermal application of a patch with musk ambrette solution in phenyl ethyl alcohol (PEA) at concentrations of 10, 40, 80, or 240 mg/kg bw/day. Clinical and haematological examinations were conducted after six and 12 weeks. Necropsy revealed depressed testicular weight and testicular tubular degeneration in animals receiving 240 mg/kg bw/day.

Public exposure

While no Australian use information is available, the chemical is reported to be used as a fragrance ingredient in cosmetic and domestic products at up to 2 % concentration in consumer end products.

Many countries, including the European Union, New Zealand and Canada, have prohibited the use of this chemical in cosmetic products.

Currently, there are no restrictions in Australia on using this chemical in cosmetic and or domestic products. In the absence of any regulatory controls, the characterised critical health effects (neurotoxicity and reproductive toxicity) have the potential to pose an unreasonable risk to the public in relation to the uses identified.

International regulations

The chemical is listed on the following:

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- Association of Southeast Asian Nations (ASEAN): Cosmetic Directive Annex III, part 1: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

This chemical is prohibited under the IFRA Standard (47th Amendment).

Scheduling status

Musk ambrette is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One public submission was received. The submission raised no objections to the proposal to include the substance in Schedule 10.

The public submission is available at the TGA website.

ACCS advice to the delegate

The committee recommended that a new Schedule 10/Appendix C entry be created for benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro- (musk ambrette) as follows:

Schedule 10—New Entry

BENZENE, 1-(1,1-DIMETHYLETHYL)-2-METHOXY-4-METHYL-3,5-DINITRO-

Cross reference entry: Amber Musk, Musk Ambrette

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included c) the toxicity of the substance; and f) any other matters that the Secretary considers necessary to protect public health.

The committee recommended an implementation date of 1 June 2016.

The reasons for the recommendations comprised the following:

- The substance is neurotoxic and a reproductive toxicant at low doses; and
- there is potential for public exposure to the substance due to its accumulation in the environment.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

[11] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that musk ambrette be listed in Schedule 10, to control its use as a fragrance ingredient in cosmetics and other products. Fragrance ingredients previously considered by the delegate and the ACCS may have either been listed in Schedules 5 or 6 because of their skin sensitising potential. In some cases, scheduling was not considered to be necessary based on the very low concentrations expected to be used in products. Musk ambrette warrants the more stringent controls available via listing in Schedule 10 because of demonstrated neurotoxicity and testicular toxicity in rat studies at relatively low doses applied dermally. The delegate agrees that the Schedule 10 listing be made under the chemical name 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene, with the common name musk ambrette included in parenthesis and a cross reference to amber musk added to the index of the Poisons Standard.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* to be (c) the toxicity of a substance.

The proposed implementation date is **1 June 2016**.

Because of the potential health risks associated with any continued use of this fragrance ingredient in products in Australia, and the fact that its use is prohibited in some overseas jurisdictions, the earliest possible implementation date is warranted.

Schedule entry

Schedule 10—New Entry

1-(1,1-DIMETHYLETHYL)-2-METHOXY-4-METHYL-3,5-DINITROBENZENE- (musk ambrette)

Cross reference entry in Index: Amber Musk

1.12 Oxathiapiprolin

Scheduling proposal

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

- In August 2015, the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to approve a new active constituent, recommends that the Delegate consider creating a new entry for oxathiapiprolin Appendix B of the SUSMP.

Scheduling application

The reasons for the request are:

- The applicant submitted a data package seeking approval of the new active constituent oxathiapiprolin, a member of the piperidinyl thiazole isoxazoline class of chemical. As a new chemical for AgVet use, it will require consideration by the Delegate/ACCS for SUSMP listing prior to final registration of products containing this active constituent.
- Currently proposed products attached to this application are for agricultural use.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS support the OCS proposal that the toxicity profile of oxathiapiprolin is low and that listing in Appendix B is warranted?

- Noting that a GP maximisation test on the active ingredient was negative for sensitisation potential, but that a similar test on the formulated product was positive, does this suggest that oxathiapiprolin should be listed in Schedule 5 or 6? Is there any clear basis for the disparity in the sensitisation test results?
- Do the OCS-recommended safety directions, that include warnings of sensitisation potential, obviate the need to schedule the active ingredient?

Substance summary

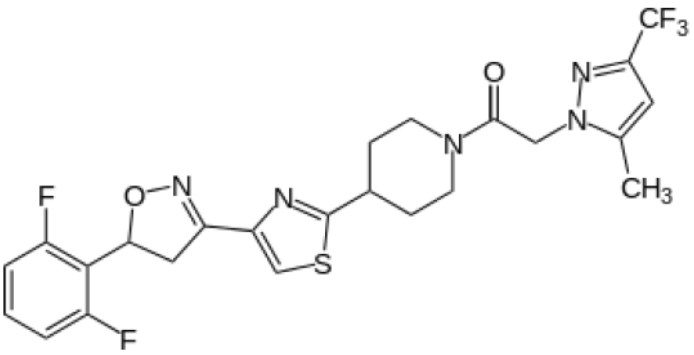


Figure 9. Chemical structure of Oxathiapiprolin (DPX-QGU42)

Acute toxicity

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

Toxicity	Species	Oxathiapiprolin	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	SD Rat	>5000 (no deaths)	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	SD Rat	>5000 (no deaths)	Appendix B
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	SD Rat	>5100 (no deaths)	Appendix B
Skin irritation	NZW rabbit	Non-irritant	Appendix B
Eye irritation	NZW rabbit	Non-irritant	Appendix B
Skin sensitisation (GPMT method)	Hartley Guinea pigs	Not sensitising	Appendix B

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

For full summaries and discussion of other endpoints, please see the OCS evaluation report for oxathiapiprolin/the product. An abridged overview is included below.

Repeat-dose toxicity

Short-term and subchronic toxicity studies in rats, mice and dogs reported no systemic toxicity effects of oxathiapiprolin. Chronic dietary studies in mice and rats also reported no systemic toxicity. No treatment related adverse effects were seen in a short-term dermal study in the rat at the limit dose.

Mutagenicity/Genotoxicity

There was no evidence of a mutagenic/genotoxic potential of oxathiapiprolin or its primary metabolites in vitro with and without metabolic activation, or a genotoxic potential in vivo. While the metabolite IN-E8S72 was positive in vitro for structural chromosome aberrations in human peripheral blood lymphocytes, the follow-up in vivo micronucleus test with IN-E8S72 was negative at up to the limit dose of 2000 mg/kg bw.

Carcinogenicity

There was no evidence of carcinogenic potential in the long-term rodent tests.

Reproduction and developmental toxicity

In a dietary two generation study in rats, no parental toxicity was seen and no effect was seen on reproductive parameters. However, there was a slight but significant increase in the mean age to achieve preputial separation in these F1 and F2 males at the highest dose of 17000/10000 ppm (equivalent to 1228/1278 mg/kg bw/day). This singular effect of a delay in preputial separation, associated with decreases in pup body weight at 17000/10000 ppm, a dose level exceeding the limit dose of 1000 mg/kg bw/day (as recommended in the OECD TG 416), occurred without other evidence of reproductive/developmental toxicity across the series of Guideline-compliant studies. No evidence of developmental toxicity potential was seen in an oral (gavage) developmental toxicity study in rats or in rabbits, and androgenic potential of oxathiapiprolin was negative in a series of in vivo and in vitro studies). Therefore, while acknowledging the occurrence of the preputial separation finding, the available data suggests that oxathiapiprolin should not being considered a hazard for reproductive or developmental toxicity.

Other toxicology endpoints

In an acute oral (gavage) neurotoxicity study in rats no evidence of an acute neurotoxic effect was seen in functional observation battery or motor activity assessment. Oxathiapiprolin was also not neurotoxic in rats in the combined subchronic toxicity/neurotoxicity study at up to limit dose concentrations.

Oxathiapiprolin is not considered to pose any immunotoxicity risk.

Observation in humans

No information was provided.

Public exposure

At this time, the proposed agricultural use of oxathiapiprolin is not expected to result in general public (i.e. domestic) exposure. Spray drift considerations have not been considered.

International regulations

Oxathiapiprolin is part of a Global Joint Review (US EPA as lead with Health Canada, Australia and Mexico as partners) and is currently under national assessment for each individual country. The US EPA has notified a proposed registration decision in July 2015.

Scheduling status

Oxathiapiprolin is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

No public submissions were received.

ACCS advice to the delegate

The Committee recommended that a new Appendix B listing be created for oxathiapiprolin as follows:

Appendix B—New Entry

OXATHIAPIPROLIN

The committee recommended an implementation date of 1 June 2016.

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; (c) the toxicity of a substance.

The reasons for the recommendations comprised the following:

- active constituent in pesticide products; and
- very low toxicity

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that oxathiopiprolin has sufficiently low toxicity that it does not meet any of the SPF criteria for scheduling. Accordingly, listing in Appendix B is considered to be appropriate. The delegate notes that the ACCS was unable to resolve the apparent difference in sensitisation potential between the active ingredient and the tested product, but notes that the Safety Directions provide adequate warning for users of the product and that listing in Schedule 5 is not necessary to flag this unresolved potential toxicity.

The proposed addition to the SUSMP is **1 June 2016**.

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

Appendix B—New Entry

OXATHIAPIPROLIN

Part 1 –Reasons for Entry

[12] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

a) Low toxicity

Part 2 – Area of Use

1.3 Fungicide.

1.13 *p*-Methylaminophenol

Scheduling proposal

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

- A proposal to create a new entry for *p*-methylaminophenol and its sulfate salt in Schedule 6 to include use in hair dyes and eyelash colouring products with an appropriate cut-off.

Scheduling application

In August 2015, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the proposal to be considered by the delegate for inclusion in the Poisons Standard.

The reasons for the request are:

- *p*-methylaminophenol sulfate has reported cosmetic use in permanent hair dye preparations in Australia;
- the chemicals are moderate to severe skin sensitisers;
- only limited data are available on eye and skin irritation; a 3 % concentration of the chemicals may have slight eye and skin irritation potential;
- the chemicals are expected to cause serious health effects following repeated oral exposure;
- international restrictions for use of the chemicals in hair dyes (European Union— the maximum concentration allowed is 0.68 % after mixing under oxidative conditions).

The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of sensitisation even below the overseas restriction cut-off, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical below the concentration cut-off. These chemicals have similar use and hazard profiles to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of *p*-methylaminophenol (acute toxicity, equivocal mutagenicity, skin-eye irritancy and moderate-severe sensitisation potential) warrants controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of moderate-severe skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including *p*-methylaminophenol in Schedules 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 0.68% (EU regulation) or 1% (rounded)? Should there be no cut-off, based on the sensitisation potential?

- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Although there are no notified commercial uses other than in cosmetics, should a Schedule 6 listing be specific for use in hair dyes or cosmetic products (as for some other hair dye ingredients)?
- What name should be used for any schedule entry – *p*-methylaminophenol; methyl-p-aminophenol; 4-(methylamino) phenol; N-methyl-4-aminophenol or metol?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

This report, containing more detailed information about the substance, is publicly available on the NICNAS website.

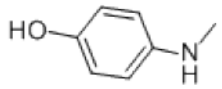


Figure 10. Chemicals structure of *p*-methylaminophenol

Acute toxicity

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

Toxicity	Species	*p*-methylaminophenol and its sulfate salt	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Mouse	380	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	-
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	-
Skin irritation	Rabbit	Slight irritant at 3 % (limited data)	-
Eye irritation	Rabbit	Slight irritant at 3 % (limited data)	-
Skin sensitisation (LLNA)	Mouse	Moderate to severe skin sensitiser (EC3 = 2.2%)	Schedule 6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Skin sensitisation

The chemicals are considered to be moderate to severe skin sensitisers according to the SPF classification.

The skin sensitising potential of *p*-methylaminophenol sulfate was investigated in a local lymph node assay (LLNA). A solution containing the chemical at 0.25, 0.5, 1, 2.5 or 5 % was applied (25 µL) to the dorsal surface of both ears of CBA/J mice, once daily for three days. The treated animals were

monitored daily for mortality and clinical signs. The study reported a dose-related increase in the stimulation index (SI), with 2.5 % and 5 % concentrations, exceeding the value of three. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 2.2 %, indicating the chemical as a moderate to severe skin sensitiser.

In a skin sensitisation test, albino Hartley guinea pigs (n = 10/sex) were treated topically (occlusive, behind the right shoulder blade) with 0.5 g of *p*-methylaminophenol, three times per week for three weeks and once on week four. The animals also received two intradermal injections of Freund's complete adjuvant on days one and 10. Twelve days after induction, the untreated left flank was challenged with 0.5 g of the chemical for 48 hours under occlusion. No skin reactions were observed.

Although a guinea pig skin sensitisation study with *p*-methylaminophenol gave negative results, based on the positive results observed for *p*-methylaminophenol sulfate in a more reliable assay, both chemicals are expected to be skin sensitisers.

Repeat-dose toxicity

Based on the data available for *p*-methylaminophenol sulfate, the chemicals are expected to cause serious damage to health from repeated oral exposure. In a 13-week oral gavage study, SD rats were dosed with *p*-methylaminophenol sulfate (suspended in 0.5 % carboxymethylcellulose) at 0, 3, 10, or 30 mg/kg bw/day. A no observed adverse effect level (NOAEL) of 10 mg/kg bw/day was reported based on tubular epithelial degeneration/single cell necrosis in the kidneys of most males and in half of the female rats at 30 mg/kg bw/day. In addition, some males of this group had higher urinary volumes with lower specific gravity. However, these changes were reported as completely reversible within the four-week recovery period.

No information was available for repeated dose toxicity by inhalation route and dermal routes.

Genotoxicity

The available data are not sufficient to derive a conclusion on the genotoxicity of the chemicals.

Carcinogenicity

Only limited data are available. The chemicals are not expected to be carcinogenic via dermal exposure at 1 % concentration.

Reproductive and developmental toxicity

Based on the limited data available, the chemicals are not known to cause reproductive or developmental toxicity.

Public exposure

Considering the use of these chemicals in permanent hair dyes in Australia, the main route of public exposure is expected to be through the skin.

The Association of Southeast Asian Nations (ASEAN), European Union (EU) and New Zealand have restricted the use of these chemicals in cosmetics. Following a safety evaluation, the SCCP (2006) concluded that the 'use of *p*-methylaminophenol sulphate itself as an oxidative hair dye at a maximum concentration of 0.68% in the finished cosmetic product (after mixing with hydrogen peroxide) does not pose a risk to the health of the consumer, apart from its sensitising potential.'

Currently, there are no restrictions in Australia on using these chemicals in cosmetics or hair dyes. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk for the uses identified.

International regulations

The chemicals are listed on the following:

- ASEAN Cosmetic Directive Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down—'after mixing under oxidative conditions, the maximum applied to hair must not exceed 0.68 % (as sulphate)'; Under 'wording and conditions of use and warnings' indicated to include 'Hair colourants can cause severe allergic reactions'; and
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

Scheduling status

p-Methylaminophenol and its sulfate are not specifically scheduled.

Scheduling history

p-Methylaminophenol and its sulfate have not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received.

No objections to aligning with EU were raised. It was noted in the submission that it is important to maintain "in-use" concentrations for hair dye preparations, due to the mode of use being mixing with an oxidising substance prior to use.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee recommended that new Schedule 6 and Appendix F entries for p-methylaminophenol be created with exceptions or cut-offs as follows:

Schedule 6—New Entry

p-METHYLAMINOPHENOL except when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less after mixing for use 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 sensitisation to certain individuals. 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 F—New Entry

p-METHYLAMINOPHENOL

Part 1, Warning Statement: 28

The ACCS recommended an implementation date of 1 June 2016.

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

The reasons for the recommendations comprised the following:

- The substance is used in hair dye products
- The substance has potential for skin sensitisation and acute oral toxicity and therefore fits the criteria for inclusion in Schedule 6
- Its use at low concentrations can be managed by reverse scheduling labelling requirements in hair dye products

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[13];
- Other relevant information.

Delegate's interim decision

Oxidative hair dyes of the aromatic diamine and aminophenolic classes have some common toxicological properties that warrant controls over scheduling. These features are primarily skin-eye irritancy and sensitization potential. These toxicological properties generally align with SPF criteria for listing in Schedule 6. Several of these dyes (e.g. phenylenediamines, toluenediamines; aminophenols) have already been listed in Schedule 6, but previous scheduling policies have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitization, and recommending testing for individual susceptibility before use. This approach is commonly called 'reverse scheduling'. Where there is potential mutagenicity, or the need to prevent uses for skin colouration (tattooing) or use to dye eyebrows or eyelashes, some of these substances have been listed in Schedule 10 to prevent such uses.

This is one of six oxidant hair dyes that were referred to the November 2015 meeting of the ACCS for advice to the delegate on scheduling. The key issues were whether their toxicological profiles sufficiently match the SPF criteria for inclusion in Schedule 6 and whether product exemptions based on 'reverse scheduling' could be applied, consistent with labelling provisions applied to other oxidative hair dyes. Given that some products containing oxidative hair dyes require mixing with an oxidant, such as hydrogen peroxide, before application to the hair, consideration was given to appropriate exemption cut-off concentrations that take account of the final concentration applied to the hair.

The delegate notes, and accepts, ACCS advice that *p*-methylaminophenol should be listed in Schedule 6, with an exemption cut-off at 1%, provided products are labelled with the warning statements about potential skin sensitisation that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that warning statements relating to use for dyeing eyebrows and eyelashes are not needed, because the substance is not a strong irritant. The delegate also notes ACCS advice that p-methylaminophenol is the INCI name and is the preferred name for listing in Schedule 6.

The proposed implementation date is **1 October 2016**.

[13] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

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

Schedule entry

Schedule 6—New Entry

p-METHYLAMINOPHENOL except when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of *p*-methylaminophenol after mixing for use 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 sensitisation to certain individuals. 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 F—New Entry

p-METHYLAMINOPHENOL

Part 1, Warning Statement: 28

1.14 Schedule 5 Paint Amendment

Scheduling proposal

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

- In August 2015, a proposal was submitted to the delegate to consider amending Part 2 - 1.5.8 of the Poisons Standard to remove the labelling exemption for Schedule 5 paints and tinters.

Scheduling application

The reasons for the request were:

- The applicant contends that the Part 1.3 exemption for Schedule 5 paints is masking the true hazards of oil based paints from the consumer market. With the introduction of Globally Harmonised System (GHS) the visual difference of how a tin of paint is marketed is getting larger and it is believed that this will lead industrial/professional users to use consumer products without adequate safety precautions as they appear safer.

Specific issues/questions raised by the delegate

The SPF requires consultation with the States/territories on amendments to Parts 1-3 of the Poisons Standard. At the time of referral, the delegate believed that such consultation could be achieved via referral to a meeting of the ACCS. The ACCS advice was that a more formal consultative proposal may be needed. The delegate had raised the following issues in the referral to the ACCS.

- The applicant seeks to amend the current Part 2 Clause 1.5.8 exemptions so that all paints and tinters are labelled only in accordance with the GHS labelling provisions in workplace requirements contained in the *Labelling of Workplace Hazardous Chemicals – Code of Practice – December 2011.* This would have the effect of removing exemptions for paints containing Schedule 5 substances,

and substituting label warnings statements depending on whether the paints contain substances in the First and Second Group of Part 2, Section 7 (formerly Appendix I).

- The applicant's proposal essentially seeks to deliver a position where paint companies will label consumer products according to the GHS, claiming that there is no benefit in dual labelling/split filling products; and that paint companies will develop safer paints to avoid hazard statements/signal words occurring; and that consumers will be better informed in the risks that paints pose even if labelled according to the SUSMP.
- The ACCS may wish to note that the matter of a potential conflict between labelling requirements under State-territory laws for consumer products and requirements under industrial laws have been previously addressed. Where there may be potentially overlapping regulatory requirements for dual use products (i.e. those with both workplace and domestic use) there has been agreement that dual use products must comply with the requirements of the SUSMP.

The delegate asked the committee the following questions:

- Does the ACCS support the proposed changes to labelling provisions for paints and tinters? If so, what rationale does the ACCS propose in support of such a recommendation?
- To what extent would proposed GHS labelling provide unambiguous additional information to consumers, beyond information currently required in the Poisons Standard.

If the ACCS does support the proposed amendment, what implementation date is proposed to allow for an orderly re-labelling of existing products?

Background

Currently paints and tinters that contain only Schedule 5 poisons are exempt from the labelling requirements of Section 1.3 of the Poisons Standard. As such, the predominate hazard information on a consumer paint tin is the Dangerous Goods information.

The paint industry is going through a relabelling exercise to meet the 1 January 2017 deadline for all industrial/commercial products to be labelled according to Globally Harmonised System (GHS) of Classification and Labelling of Chemicals as required by the model Work Health and Safety. GHS labelling information is more prominent than existing labelling requirements as it contains both written and pictorial hazard information.

Detailed claims against the requirements of the scheduling policy framework

In the paint industry, products are commonly split-fills where the same product is sold to both consumer and trade markets in different labelled tins. Looking at how a tin of paint will be labelled for the workplace vs a tin labelled for consumer the applicant believes that the difference is getting so large that a consumer may be provided with a false sense of security.

The applicant contends that, to the consumer, the paint looks "safe" just like the old fashion oil based paints, but to the worker the paint looks highly hazardous and full PPE and precautions are required. The applicant believes that the consumer will be complacent in it use and expose themselves to unnecessary risk and a worker will be more inclined to purchase consumer labelled products as they appear safer and will miss receiving appropriate hazard information.

The three outcomes that are foreseen by the applicant as occurring if Part 2 is amended as proposed are:

1. paint companies will label consumer products according to GHS as there is no benefit in dual labelling/split filling products;
2. paint companies will develop safer paints to avoid hazard statements/signal words occurring; and,

3. consumers will be better informed in the risks that paints pose even if labelled according to SUSMP.

Scheduling status

1.5.8 Paints

1. The requirements of Section 1.3 do not apply to:

    a) paint (other than a paint for therapeutic or cosmetic use) which:

        i. contains only Schedule 5 poisons; or

        ii. is a First Group or Second Group paint that is labelled with:

            A. the word "WARNING", written in bold-face sans serif capital letters, the height of which is not less than 5 mm, on the first line of the main label with no other words written on that line; and

            B. the expression "KEEP OUT OF REACH OF CHILDREN", written in bold-face sans serif capital letters, the height of which is not less than 2.5 mm, on a separate line immediately below the word "WARNING"; and

            C. the appropriate warnings specified for the paint in Appendix F, written immediately below the expression "KEEP OUT OF REACH OF CHILDREN"; and

            D. the name and proportion of the First Group or Second Group poisons it contains, provided that where the substance is a metal or metal salt the proportion is expressed as the metallic element present "calculated on the non-volatile content" or "in the dried film" of the paint; or

    b) a tinter which contains:

        i. only Schedule 5 poisons; or

        ii. a poison included in the First Group or Second Group in Part 2 Section 7, provided that it is labelled with the name and proportion of that poison, and where the poison is a metal or metal salt, the proportion is expressed as the metallic element present as "calculated on the non-volatile content" or "in the dried film".

Public pre-meeting submissions

Two public submissions were received. There were no contentions with the application to amend Part 2, 1.5.8 Paints. Both submissions asked for a long implementation date to allow for any changes to labelling.

The public submission is available at the TGA website.

ACCS advice to the delegate

The Committee suggested that the current scheduling of Schedule 5 Paints remains appropriate, although it declined to make a firm recommendation to the Delegate, pending the outcome of formal negotiations on scheduling policy issues related to amendment of Parts 1-3 of the Poisons Standard.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate has decided to defer making a decision on this issue, pending formal consultation with the States/Territories, as required in the new AHMAC Scheduling Policy Framework for amendments to Parts 1-3 of the Poisons Standard.

1.15 Topramezone

Scheduling proposal

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

- In September 2015, the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to approve a new active constituent, recommends that the Delegate consider creating a new entry for topramezone in Schedule 6 of the SUSMP.

Scheduling application

The reasons for the request were:

- The applicant submitted a data package seeking approval of the new active constituent topramezone, an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase (4 HPPD), the second enzyme in the tyrosine catabolic pathway. As a new chemical for AgVet use, it will require consideration by the Delegate/ACCS for SUSMP listing prior to final registration of products containing this active constituent.
- There is currently no proposed product attached to this application however, there are indications that topramezone will be incorporated into herbicidal products to be used on food-producing crops (EFSA, 2014).

Specific issues/questions raised by the delegate

The delegate asked the committee the following questions:

- The delegate notes that much of the toxicity profile of topramezone (acute toxicity, skin/eye irritancy and sensitisation potential) is consistent with listing in Schedule 5 or exempt from scheduling. However, the OCS recommendation for listing in Schedule 6 is based primarily on findings of a low incidence of developmental toxicity in a rabbit study, in the absence of any apparent maternal toxicity. Does the ACCS support this as a basis for listing in Schedule 6?
- The OCS evaluation of the observed thyroid carcinogenicity and corneal opacities in rats suggests that these findings are not of significance for scheduling purposes. Does the ACCS agree with this evaluation?

[14] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

To what extent is the toxicity of topramezone consistent with that of other HPPD inhibitors (e.g. mesotrione – listed in Schedule 5 in 2011)?

Substance summary

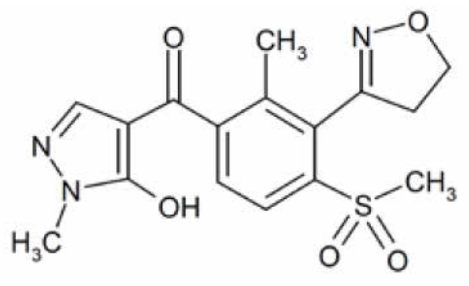


Figure 11: Chemical structure of topramezone (BAS 670 H)

Acute toxicity

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

Toxicity	Species	Topramezone	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Wistar Rat	>2000 (no deaths)	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Wistar Rat	>2000 (no deaths)	Appendix B
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Wistar Rat	>5050 (no deaths)	Appendix B
Skin irritation	NZW rabbit	Slight irritant	Schedule 5
Eye irritation	NZW rabbit	Slight irritant	Schedule 5
Skin sensitisation (GPMT)	Guinea pig	Non-sensitising	Appendix B

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

For full summaries and discussion of other endpoints, please see the OCS evaluation report for topramezone. An abridged overview is included below.

Repeat-dose toxicity

In repeat-dose toxicity studies, the rat appeared to be the most sensitive species, with the thyroid gland (increased incidence and/or severity of flaky colloid, follicular cell hypertrophy and follicular cell hyperplasia), pancreas (diffuse degeneration) and eyes (corneal opacity) as target organs for toxicity in this species, but not mice or dogs. Increased kidney and/or liver weights, generally in the absence of histopathological lesions, was evident in mice and/or dogs. Serum chemistry (all species) and urinalysis findings (rats and dogs; not assessed in mice) consistent with the pharmacological action of topramezone (4-HPPD inhibition) included elevated serum tyrosine levels and increased urinary ketone levels. While reversibility of effects was not always assessed, the nature of the toxicity findings indicates reversibility is possible. Overall, the repeat-dose toxicity profile of topramezone is very similar to other 4-HPPD inhibitors, such as mesotrione.

Mutagenicity/Genotoxicity

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

Carcinogenicity

There was no evidence of a carcinogenic potential in an 18-month carcinogenicity study in mice by dietary administration up to and including the highest dose tested of 1903/2467 mg/kg bw/day (8000 ppm) for males/females, respectively.

In a rat dietary oral carcinogenicity study, an increased incidence of thyroid gland tumours (follicular cell adenoma and carcinoma; both sexes) with an increased incidence of follicular cell hyperplasia was observed in females only. The Mode of Action data did indicate that topramezone treatment causes a perturbation of thyroid-pituitary hormone homeostasis, which is a potentially underlying cause for thyroid tumour formation in rats. Thyroid tumours in rodents that occur as a result of alterations to thyroid hormone levels are generally not considered to be relevant to human subjects. Therefore, topramezone is unlikely to pose a carcinogenic risk to human subjects.

Reproductive and developmental toxicity potential

Fertility was unaffected in mice and rats in three and two generation reproduction studies, respectively.

Topramezone crossed the placenta in rabbits and elevated foetal serum levels of tyrosine were observed. There were no adverse embryofoetal developmental effects observed in mice. Similar foetal skeletal variations (delayed ossification and supernumerary ribs and/or vertebrae) were seen in rats and rabbits. These variations occurred in the absence of maternotoxicity and are considered to be secondary to the pharmacological effects of topramezone. Similar foetal skeletal effects were observed with other 4-HPPD inhibitors, such as mesotrione. These effects alone were not considered sufficient to warrant labelling of mesotrione as a developmental toxicant.

However, in both rats and rabbits, topramezone appeared to have adverse effects on kidney genesis and development in foetuses/pups following maternal exposure. Foetuses lacking a kidney/ureter were seen in developmental studies with rabbits, while F_1 pups adults and with renal pelvic dilation (a malformation) were seen in a reproductive study in rats; kidney anatomical maturation occurs postnatally in rodents.

The data from two species (rats and rabbits) suggests topramezone treatment has an irreversible effect on the developing kidney. Irreversible foetal kidney lesions have not been reported in developmental/reproductive studies with other 4-HPPD inhibitors. With the available data, this effect cannot be ruled out as not being relevant to humans. Unlike other members of the 4-HPPD inhibitor class, topramezone should be considered as a developmental toxicant.

Other toxicology endpoints

No evidence of neurotoxicity was seen in an acute and repeat dose developmental neurotoxicity study.

Topramezone was not investigated for immunotoxic potential.

Observation in humans

No information was provided.

Public exposure

At this time, no agricultural use product containing topramezone has been proposed.

International regulations

Topramezone as an active constituent as well as a SC herbicidal product containing topramezone have been approved/registered by the US EPA (2005, conditional approval), EFSA (2014) and Health Canada (2006, as a temporary approval).

Scheduling status

Topramezone is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One public submission was received. The submission was a comment on the OCS Technical Report. The submission refers to the dilated renal pelvis findings stating that these occur at maternal toxic concentrations and should be considered a variation, rather than a malformation, and are secondary to tyrosinemia. The dilated renal pelvis findings are proposed not to be human-relevant and should not be used for the derivation of reference values. The NOAEL from the developmental rabbit studies should be used instead.

The public submission is available at the TGA website.

ACCS advice to the delegate

The committee recommended that a new Schedule 5 entry be created for topramezone as follows:

Schedule 5—New Entry

TOPRAMEZONE

The Committee recommended an implementation date of 1 June 2016.

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; (c) the toxicity of a substance.

The reasons for the recommendations comprised of the following:

- active constituent for use in agvet chemicals
- the toxicological profile of topramezone fit that of other HDDP inhibitors
- inconsistent findings on developmental effects in kidneys and maternotoxicity were observed in the animal studies but the skeletal findings should constitute a hazard
- the substance meets the criteria for inclusion 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*;

- Scheduling factors[15];
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that topramezone be listed in Schedule 5, with no cut-off to exempt at this time in light of there being no product information. The delegate agrees that the overall toxicological profile of topramezone is consistent with SPF criteria for listing in Schedule 5. The equivocal nature of the foetal developmental effects, including the apparently flat dose-response relationship and their possible relationship to the elevated tyrosine levels associated with treatment with this HPPD inhibitor, were considered insufficient to require listing in Schedule 6.

The proposed implementation date is **1 June 2016**.

The earliest practicable implementation of the scheduling decision will facilitate approval of the substance by the APVMA.

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 5—New Entry

TOPRAMEZONE

[15] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

2. Scheduling proposals referred to the November 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS#16)

Summary of delegate's interim decisions

Substance	Interim decision
Bismuth oxychloride	The delegate's interim decision is that the current scheduling for bismuth oxychloride remains appropriate
Naproxen	**APPENDIX H – New entry** Proposed implementation date: 1 June 2016.
Paracetamol	Amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The Schedule 2 and Schedule 3 entries for paracetamol should be amended as follows: **Schedule 2 – Amend entry** PARACETAMOL for therapeutic use: a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a pack of not more than 3 day supply. b) in other preparations **except**: i) when included in Schedule 4. ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when: A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules. B) compliant with the requirements of the Required Advisory Statements for Medicine Labels. C) not labelled for the treatment of children 6 years of age or less. D) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin or iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or

Substance	Interim decision
	guaiphenesin or when combined with effervescent agents) when: A) packed in blister or strip packaging or in a container with a child-resistant closure. B) in a primary pack containing not more than 20 tablets or capsules. C) compliant with the requirements of the Required Advisory Statements for Medicine Labels. D) not labelled for the treatment of children 6 years of age or less and E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin. **Schedule 3 – Amend entry** PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2. Proposed implementation date: 1 June 2016.
Piracetam	The delegate's interim decision is that the current scheduling of piracetam remains appropriate.
Lansoprazole, omeprazole and rabeprazole	The delegate's interim decision is to include lansoprazole, omeprazole, rabeprazole in Schedule 2: **LANSOPRAZOLE** **SCHEDULE 2 – New entry** LANSOPRAZOLE in oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply. **SCHEDULE 3 – Amend entry** LANSOPRAZOLE in oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2. **SCHEDULE 4 – Amend entry** LANSOPRAZOLE except when included in Schedule 2 or 3. **OMEPRAZOLE** **SCHEDULE 2 – New entry** OMEPRAZOLE in oral preparations containing 20 mg or less of

Substance	Interim decision
	omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply. **SCHEDULE 3 – Amend entry** OMEPRAZOLE in oral preparations containing 20 mg or less of omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2. **SCHEDULE 4 – Amend entry** OMEPRAZOLE except when included in Schedule 2 or 3. **RABEPRAZOLE** **SCHEDULE 2 – New entry** RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply. **SCHEDULE 3 – Amend entry** RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2. **SCHEDULE 4 – Amend entry** RABEPRAZOLE except when included in Schedule 2 or 3. Proposed implementation date: 1 June 2016.
Flubromazolam	**SCHEDULE 9 – New entry** Flubromazolam Proposed implementation date: 1 June 2016.
Thymosin Beta 4 (Thymosin β4)	**Schedule 4 – New entries** Thymosin Beta 4 (Thymosin β4) TB-500 Fibroblast Growth Factors **Appendix D, Item 5 – New entries**

2.1 Bismuth oxychloride

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To exempt bismuth oxychloride for human therapeutic use from Schedule 4.

Substance summary

The applicant has provided the following information regarding Bismuth Oxychloride:

Bismuth oxychloride is a synthetically prepared white or nearly white amorphous or finely crystalline powder. Bismuth oxychloride is used in formulations of many cosmetic and personal care products, including make-up, nail products, cleansing products, fragrances and hair colouring products. Bismuth oxychloride imparts a white colour to cosmetics and personal care products.

The United States Food and Drug Administration (FDA) lists bismuth oxychloride as a colour additive exempt from certification. The FDA requires that bismuth oxychloride conforms to the following specifications and shall be free from impurities other than those named (to the extent that such other impurities may be avoided by good manufacturing practice): Volatile matter, not more than 0.5%; Lead (as Pb), not more than 20 ppm; Arsenic (as As), not more than 3 ppm; Mercury (as Hg), not more than 1 ppm; Bismuth oxychloride, not less than 98%. Bismuth oxychloride is permitted to be used to colour externally applied drugs, including those intended for use in the area of the eye. Use in lipsticks is permitted. The FDA considers that certification of bismuth oxychloride is not necessary for protection of public health.

Toxicological data presented in a journal article in 1975 provided the following summary: The pearlescent white pigment, bismuth oxychloride, which is used as a colouring agent for decorative cosmetics, was administered to BD rats in the diet in a concentration of 1, 2 or 5% for two years. Neither carcinogenic activity nor other toxic effect attributable to the test compound was detected in the animals, which were maintained on a control diet from the termination of treatment until their death.

Bismuth oxychloride was included on the Australian Register of therapeutic Goods (ARTG) in July 2002. TGA currently permits its use as an active ingredient in biologicals, and as an excipient in biologicals or medical devices. The ARTG states that bismuth oxychloride "will not be available as a starting material for OTC (products)" – this is consistent with the current scheduling of bismuth oxychloride (Schedule 4 for human therapeutic use).

The TGA regulates some sunscreens as therapeutic goods. These include primary sunscreens with SPF 4 or more, secondary sunscreens (except those regulated as cosmetics), and primary or secondary sunscreens with SPF 4 or more that contain an insect repellent. Products that contain an ingredient with sunscreening properties where the primary purpose of the product is neither sunscreening nor therapeutic ('cosmetic sunscreens') are regulated as cosmetics by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Bismuth oxychloride is not used as a UV filter, but may be included as an excipient in cosmetic products (e.g. to give makeup a shimmering effect), including cosmetic sunscreens.

In Australia, the NICNAS Inventory multi-tiered assessment and prioritisation (IMAP) framework lists the status of bismuth oxychloride (bismuthine, chlorooxo-) for cosmetic use as Tier I Final (chemicals that are not considered to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I assessment).

Scheduling status

Bismuth Oxychloride is currently covered under entries for 'BISMUTH COMPOUNDS' in Schedule 4.

SCHEDULE 4

BISMUTH COMPOUNDS for cosmetic use, **except**:

a) bismuth citrate when incorporated in hair colourant preparations in concentrations of 0.5 per cent or less; or

b) bismuth oxychloride.

BISMUTH COMPOUNDS for human therapeutic use, except bismuth formic iodide or bismuth subiodide in dusting powders containing 3 per cent or less of bismuth.

Scheduling history

Bismuth compounds

Poisons Standard (Standing) Committee: May 1979

The PSSC considered concerns that had been raised by the Australian Drug Evaluation Committee (ADEC) regarding the unrestricted availability of bismuth compounds (particularly the subnitrate and tripotassium dicitrata-bismuthate) and their potential to cause neurotoxicity.

The PSSC considered Schedule 4 appropriate, in view of limited published data on mechanism of action of bismuth compounds. The PSSC recommended that bismuth subgallate should be deleted from Schedule 4, and that 'Bismuth compounds for human oral use' should be inserted as a new entry in Schedule 4.

Poisons Standard (Standing) Committee: February 1984

The PSSC considered the scheduling of bismuth, including a proposal to exempt bismuth oxychloride from Schedule 4 when used as a pearlescent in cosmetics for external use (item 4.36). The PSSC had noted that the Japanese Government Advisory Scientific Medical Committee (the only other country that had imposed restrictions on bismuth oxychloride in cosmetics) had withdrawn its restrictions (see item 3.6). The PSSC supported exempting bismuth oxychloride from scheduling when used in cosmetics, and recommended that the Schedule 4 entry for 'Bismuth' should be amended to 'Bismuth, compounds of, for human therapeutic or cosmetic use, except: (a) bismuth citrate when incorporated in hair colorant preparations in concentrations of 0.5% w/w or less; (b) bismuth oxychloride in cosmetics; (c) bismuth formic iodide in dusting powder containing 3% or less of bismuth.

Poisons Standard (Standing) Committee: May 1979

The PSSC considered concerns that had been raised by the Australian Drug Evaluation Committee (ADEC) regarding the unrestricted availability of bismuth compounds (particularly the subnitrate and tripotassium dicitrata-bismuthate) and their potential to cause neurotoxicity. The PSSC considered Schedule 4 appropriate, in view of limited published data on mechanism of action of bismuth compounds. The PSSC recommended that bismuth subgallate should be deleted from Schedule 4, and that 'Bismuth compounds for human oral use' should be inserted as a new entry in Schedule 4.

Poisons Standard (Standing) Committee: February 1984

The PSSC considered the scheduling of bismuth, including a proposal to exempt bismuth oxychloride from Schedule 4 when used as a pearlescent in cosmetics for external use (item 4.36). The PSSC had noted that the Japanese Government Advisory Scientific Medical Committee (the only other country that had imposed restrictions on bismuth oxychloride in cosmetics) had withdrawn its restrictions (see item 3.6). The PSSC supported exempting bismuth oxychloride from scheduling when used in cosmetics, and recommended that the Schedule 4 entry for 'Bismuth' should be amended to 'Bismuth, compounds of, for human therapeutic or cosmetic use, except: (a) bismuth citrate when incorporated in hair colorant preparations in concentrations of 0.5% w/w or less; (b) bismuth oxychloride in cosmetics; (c) bismuth formic iodide in dusting powder containing 3% or less of bismuth.

National Drugs and Poisons Scheduling Committee: August 1999

The NDPSC considered recommendations from the Trans-Tasman Harmonisation of Scheduling Working Party (June 1999), and agreed that the Schedule 4 entry for Bismuth compounds should be replaced by two separate entries, covering bismuth compounds for cosmetic use and bismuth compounds for therapeutic use (it was noted that the New Zealand schedule only regulates medicines). The NDPSC therefore decided to create the following Schedule 4 new entries: 'Bismuth compounds for cosmetic use except: (a) bismuth citrate when incorporated in hair colourant preparations in concentrations of 0.5 per cent or less; or (b) bismuth oxychloride'; and 'Bismuth compounds for human therapeutic use, except bismuth formic iodide or bismuth subiodide in dusting powders containing 3 per cent or less of bismuth'.

National Drugs and Poisons Scheduling Committee: November 1999

The NDPSC supported the August 1999 decision regarding the new Schedule 4 entries for bismuth compounds.

Pre-meeting public submissions

Two submissions were received.

The supporting submission made the following main point:

- The proposed exemption for human therapeutic use should be equivalent to the exemption that is currently in place for other bismuth compounds, namely in dusting powders containing 3 per cent or less of bismuth.

The opposing submission made the following main points:

- In the absence of further details cannot support the proposed amendment to exempt.
- Bismuth oxychloride is used safely for cosmetic use; however this cannot easily be transferred for therapeutic use.

The public submissions are available at https://www.tga.gov.au/public-submissions-scheduling-matters.

ACMS advice to the delegate

The ACMS recommended that the current scheduling remains appropriate.

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

The reasons for the recommendations comprised the following:

- No information was provided to the Committee on the type of product intended to be used.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

- Scheduling factors[16];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the current scheduling for bismuth oxychloride remains appropriate.

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

The reasons for the recommendation comprised the following:

- Lack of information on the type of product intended to be used, safety data when used in therapeutic goods, and the potential of greater exposure to the substance when in a sunscreen.
- Lack of information on the type of product intended to be used, safety data when used in therapeutic goods, and the potential of greater exposure to the substance when in a sunscreen. If the substance is to be included in a primary sunscreen, then it will be used more widely, in children, over a greater surface area. At present, the safety data is related to cosmetic use only, where this use is limited - primarily by adults only, in small areas and limited usage.
- Lack of information on the type of product intended to be used, safety data when used in therapeutic goods, and the potential of greater exposure to the substance when in a sunscreen. If the substance is to be included in a primary sunscreen, then it will be used more widely, in children, over a greater surface area. At present, the safety data is related to cosmetic use only, where this use is limited - primarily by adults only, in small areas and limited usage.

2.2 Naproxen

Scheduling proposal

The medicines scheduling delegate has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- Include Naproxen in Appendix H.

Substance summary

The applicant has provided the following information regarding Naproxen:

Naproxen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. Naproxen is usually given orally as the free acid or as the sodium salt (550 mg of naproxen sodium is equivalent to about 500 mg of naproxen).

Scheduling status

NAPROXEN is currently listed in Schedules 2, 3 and 4, and in Appendix F.

SCHEDULE 2

NAPROXEN in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of 30 or less dosage units.

[16] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

SCHEDULE 3

NAPROXEN in a modified release dosage form of 600 mg of naproxen or less per dosage unit in packs of 16 or less dosage units when labelled not for the treatment of children under 12 years of age.

SCHEDULE 4

NAPROXEN except when included in Schedule 3 or in Schedule 2.

Scheduling history

Advisory Committee on Medicines Scheduling (ACMS): March 2014

Delegate decision: July 2014

The ACMS considered a proposal to include naproxen in Schedule 2 in a modified release (extended release) dosage form containing 600 mg or less of naproxen per dosage unit in packs of 16 or less dosage units, when labelled not for treatment of children under 12 years of age. The ACMS recommended, and the delegate confirmed, that those modified release naproxen preparations should be included in Schedule 3. The ACMS also recommended that the SUSMP Appendix F warnings current at that time for naproxen should apply to the new Schedule 3 dosage form for naproxen. The implementation date for the delegate's decision was 1 October 2014.

Advisory Committee on Medicines Scheduling (ACMS): November 2014

Delegate decision: March 2015

The ACMS considered a proposal to include naproxen (when in Schedule 3) in Appendix H. The ACMS recommended, and the delegate confirmed, that the current scheduling of naproxen remained appropriate. Reasons for the delegate's March 2015 decision included that: Schedule 2 naproxen products can be advertised to consumers and there does not appear to be any additional benefit in advertising modified release naproxen; concern that advertising Schedule 3 products might encourage consumers to request the modified release product when conventional lower dose product might be more appropriate; and that modified release naproxen had only recently been included in Schedule 3, and there were no Schedule 3 naproxen products on the ARTG and consequently no experience with their marketing/use in Australia.

Pre-meeting public submissions

Four public submissions were received.

The main points of the supporting decisions were:

- Schedule 2 naproxen has been available for 20 years, during which related products have been advertised. This has not lead to inappropriate use or misuse by consumers.
- As the Schedule 3 entry is for a once per day dosage form, the public would benefit from knowing that there is a pain relief option with an easy to follow dosage regimen.
- There is a lower daily dose of naproxen with the Schedule 3 product.
- The availability of a pharmacist at point of sale means consumers will be made aware verbally, in addition to product labelling, of the single dose of the product.
- The advice from the pharmacist, together with appropriate warning statements on labelling and the availability of the CMI will help ensure that consumers have the information they need to manage the use of this product for the short term relief of pain.
- Schedule 3 pack size limit provides for continuous therapy for over two weeks. This supports the need for intervention by pharmacists to ensure modified-release naproxen can be used safely and optimally.

- Diclofenac, another non-steroidal anti-inflammatory medicine which has similar pharmacological properties and risk profile, has been listed on Appendix H since August 2001.

The main point of the opposing submission was:

- No new data is available in the published literature to revert the prior decision. The reasons for the prior rejections in relation to naproxen remain relevant and should be given due consideration in any decisions relating to the current application.

ACMS advice to the delegate

The ACMS recommended that naproxen should be listed in Appendix H.

The committee recommended an implementation date of 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- There is a public health benefit to advertising and there will not be inappropriate use.
- The recommendation is consistent with diclofenac's Appendix H inclusion.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to include Naproxen in Appendix H.

The proposed implementation date is 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; and c) the toxicity of the substance.

The reasons for the recommendation comprised the following:

- Public health benefit to advertising and that there will not be inappropriate use.
- Public health benefit to advertising and that there will not be inappropriate use.
- Public health benefit to advertising and that there will not be inappropriate use.

[17] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Schedule entry

APPENDIX H – New entry

2.3 Paracetamol/ibuprofen

Scheduling proposal

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

- To amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less.

Substance summary

The applicant has provided the following information regarding Paracetamol/ibuprofen:

Paracetamol

Paracetamol is a p-aminophenol derivative, which has analgesic and antipyretic effects and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain and for fever. It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever.

The usual oral dose of paracetamol in adults and children aged 12 years and older is 500 to 1000 mg every 4 to 6 hours as needed, up to a maximum of 4 g daily.

Paracetamol is in pregnancy category A.

Ibuprofen

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, post-operative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft tissue disorders such as sprains and strains. It is also used to reduce fever.

Paracetamol and Ibuprofen

The RASML requires that the labels of combination products include all the RASML statements that apply for each individual active ingredient. Therefore, the labels of OTC paracetamol/ ibuprofen combination products require the RASML statements that are required for scheduled paracetamol products and the RASML statements that are required for scheduled ibuprofen products.

Scheduling status

Paracetamol in combination with ibuprofen is currently included in Schedule 3 and 4.

Paracetamol is currently listed in Schedules 2, 3 and 4.

SCHEDULE 2

PARACETAMOL for therapeutic use **except**:

a) when included in Schedule 4.

b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

i) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules.

ii) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

iii) not labelled for the treatment of children 6 years of age or less.

iv) not labelled for the treatment of children under 12 years of age when combined with

v) phenylephrine and/or guaiphenesin or

c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

i) packed in blister or strip packaging or in a container with a child-resistant closure.

ii) in a primary pack that contains not more than 20 tablets or capsules.

iii) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

iv) not labelled for the treatment of children 6 years of age or less.

v) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin or

SCHEDULE 3

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less.

SCHEDULE 4

PARACETAMOL:

a) when combined with aspirin or salicylamide or any of their derivatives except when separately specified in the Schedules.

b) when combined with ibuprofen in a primary pack containing more than 30 dosage units.

c) in slow release tablets or capsules containing more than 665 mg paracetamol.

d) in non-slow release tablets or capsules containing more than 500 mg paracetamol.

e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol or

f) for injection.

PARACETAMOL is also currently listed in Appendix F.

IBUPROFEN is currently listed in Schedules 2, 3 and 4.

SCHEDULE 2

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

a) in liquid preparations when sold in the manufacturer's original pack containing 8 grams or less of ibuprofen.

b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units except when:

i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent).

ii) packed in blister or strip packaging or in a container with a child-resistant closure.

iii) in a primary pack that contains not more than 25 dosage units.

iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

v) not labelled for the treatment of children 6 years of age or less.

vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

SCHEDULE 3

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:

a) with a recommended daily dose of 1200 mg or less of ibuprofen.

b) not for the treatment of children under 12 years of age, except when included in or expressly excluded from Schedule 2.

SCHEDULE 4

IBUPROFEN **except**:

a) when included in or expressly excluded from Schedule 2 or 3. or

b) in preparations for dermal use.

[Refer also to the Schedule 3 entry for Paracetamol, and to point (b) of the Schedule 4 entry for Paracetamol.]

IBUPROFEN is also currently listed in Appendix F.

Scheduling history

Paracetamol / ibuprofen combinations

National Drugs and Poisons Schedule Committee (NDPSC): June 2010

Delegate Final Decision: August 2010

The NDPSC considered the scheduling of paracetamol in combination with ibuprofen in June 2010. At that time, divided dose combinations containing up to 200 mg ibuprofen + 500 mg paracetamol were included in Schedule 2 (when labelled with a maximum daily dose of 1200 mg ibuprofen, and in packs of up to 100 dosage units). The NDPSC recommended, and the delegate confirmed, that the scheduling of ibuprofen and paracetamol that was current at that time remained appropriate.

Advisory Committee on Medicines Scheduling (ACMS): February 2011

Delegate Final Decision: June 2011

The ACMS considered a proposal from the Advisory Committee on Non-prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination.

The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice.

Advisory Committee on Medicines Scheduling (ACMS): October 2012

Delegate Final Decision: February 2013

The ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less, and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

Pre-meeting public submissions

Five submissions were received.

Submissions supporting noted:

- Direct "to consumer" advertising of these combination products will be facilitated.
- The individual components have a long history of use and a well-documented, favourable safety profile.
- There is a public health benefit in consumer awareness of alternative options for relief of mild to moderate pain conditions.
- Unintentional overdose can be managed through product labelling and pharmacists being available at point of sale.
- There is little evidence of dependence, abuse, misuse or illicit use of the combination paracetamol and ibuprofen product.
- Combination products should only be indicated for children aged 12 years and up.
- Given the smaller pack size of combination products compared to single ingredient paracetamol and ibuprofen products, a potential benefit is that consumers will use less of these products over a shorter period of time.
- Pharmacy assistants are able to provide advice to consumers regarding the suitability and appropriateness of using a combination product and can refer to the pharmacist where required.

Submissions opposed noted:

- The use of paracetamol in combination with ibuprofen is not considered to be first-line therapy for the treatment of mild to moderate pain.
- A responsible quality use of medicines approach is to retain paracetamol–ibuprofen combinations in Schedule 3. This will facilitate a consistent environment where pharmacists can consider the most appropriate over-the-counter analgesic medicine (including consideration of paracetamol–ibuprofen combination products) and provide tailored advice for consumers.

- Delegate's reasons for not supporting Appendix H proposal for advertising S3 paracetamol/ibuprofen.
- Concerns regarding safety, particularly with respect to gastrointestinal bleeding and perhaps renal adverse effects.
- Pharmacists can recommend a paracetamol/ibuprofen combination product to consumers who request S3 CCA for pain relief. Rather than advertise to consumers, it is considered that paracetamol-ibuprofen combination analgesics products should be better promoted to pharmacists. Approving this scheduling proposal circumvents these concerns.
- Buying multiple small packs would not flag the need for pharmacist intervention.
- The proposed scheduling change would too easily result in inconsistencies and potential for abuse that is more than adequately catered for in the current scheduling.
- No new data is available in the published literature to revert the prior decision. The reasons for the prior rejections in relation to paracetamol/ibuprofen combination analgesics remain relevant and should be given due consideration in any decisions relating to the current application.

The public submissions are available at https://www.tga.gov.au/scheduling-delegates-decisions-public-submissions.

ACMS advice to the delegate

The ACMS recommended that paracetamol should be included in schedule 2 when combined with ibuprofen, in packs containing 12 dosage units or less.

The ACMS recommended an implementation date of 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- Risks: Adverse events as stated in the CCDS / PI documents: mainly risks in the elderly, those with GI conditions e.g. ulcer, bleeding with previous NSAID use; cardiovascular conditions, renal insufficiency, hepatic failure, asthma/hypersensitivity. Also – concomitant use of NSAIDs & other paracetamol products, interactions with other drugs
- Benefits: Effective combination, low risk of diversion/abuse/addiction, provides an option for short term use for moderate pain; the combination itself uses lower doses of each active ingredient and also provides less IBU & paracetamol in each pack.
- Purposes and extent of use of the substance: - Temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches & pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, & aches and pains associated with colds & flu.
- Dose: Nuromol: 1 tablet three times / day (maximum 3 tablets/day as per labelling; PI not supplied by applicant however the CCDS was provided). In the UK, maximum daily dose is 6 tablets as the dose is 1-2 tablets three times/day; Maxigesic: 1-2 tablets every 6 hours (maximum 8 tablets/day). This represents a maximum of either 3 or 4 days' supply.
- Well established safety profile (as described in PSUR) – relating to the safety profile of each of the individual active ingredients.
- The following Australian registered products contain this combination:

- Nuromol – AUST R 225322, Ibuprofen 200mg + Paracetamol 500 mg
- Maxigesic – AUST R 218785, Ibuprofen 150mg + Paracetamol 500 mg

· Dose: Nuromol: 1 tablet three times / day (maximum 3 tablets/day as per labelling; PI not supplied by applicant however the CCDS was provided). In the UK, maximum daily dose is 6 tablets as the dose is 1-2 tablets three times/day; Maxigesic: 1-2 tablets every 6 hours (maximum 8 tablets/day).

· 3 day supply considered appropriate for Schedule 2.

· No potential for diversion, addiction or illicit use.

Delegate's considerations

The delegate considered the following in regards to this proposal:

· Scheduling proposal;

· Public submissions received;

· ACMS advice;

· Section 52E of the *Therapeutic Goods Act 1989*;

· Scheduling factors[18];

· Other relevant information.

Delegate's interim decision

The delegate's interim decision is amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less as per the below proposed wording for the schedule entries.

The Schedule 2 and Schedule 3 entries for paracetamol should be amended as follows:

Schedule 2 – Proposed Amendment

PARACETAMOL for therapeutic use:

a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a pack of not more than 3 day supply.

b) in other preparations **except**:

   i) when included in Schedule 4.

   ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

      A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules.

      B) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

      C) not labelled for the treatment of children 6 years of age or less.

[18] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

D) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

A) packed in blister or strip packaging or in a container with a child-resistant closure.

B) in a primary pack containing not more than 20 tablets or capsules.

C) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

D) not labelled for the treatment of children 6 years of age or less and

E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin.

Schedule 3 – Proposed Amendment

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.

The proposed implementation date is 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- Risks: Adverse events as stated in the CCDS / PI documents: mainly risks in the elderly, those with GI conditions e.g. ulcer, bleeding with previous NSAID use; cardiovascular conditions, renal insufficiency, hepatic failure, asthma/hypersensitivity. Also – concomitant use of NSAIDs & other paracetamol products, interactions with other drugs

- Benefits: Effective combination, low risk of diversion/abuse/addiction, provides an option for short term use for moderate pain; the combination itself uses lower doses of each active ingredient and also provides less IBU & paracetamol in each pack.

- Purposes and extent of use of the substance: - Temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches & pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, & aches and pains associated with colds & flu.

- Dose: Nuromol: 1 tablet three times / day (maximum 3 tablets/day as per labelling; PI not supplied by applicant however the CCDS was provided). In the UK, maximum daily dose is 6 tablets as the dose is 1-2 tablets three times/day; Maxigesic: 1-2 tablets every 6 hours (maximum 8 tablets/day). This represents a maximum of either 3 or 4 days' supply.

- Well established safety profile (as described in PSUR) – relating to the safety profile of each of the individual active ingredients.

- The following Australian registered products contain this combination:

  – Nuromol – AUST R 225322, Ibuprofen 200mg + Paracetamol 500 mg

  – Maxigesic – AUST R 218785, Ibuprofen 150mg + Paracetamol 500 mg

- Dose: Nuromol: 1 tablet three times / day (maximum 3 tablets/day as per labelling; PI not supplied by applicant however the CCDS was provided). In the UK, maximum daily dose is 6 tablets as the dose is 1-2 tablets three times/day; Maxigesic: 1-2 tablets every 6 hours (maximum 8 tablets/day).
- 3 day supply considered appropriate for Schedule 2.
- No potential for diversion, addiction or illicit use.

Schedule entry

PARACETAMOL for therapeutic use:

a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a pack of not more than 3 day supply.

b) in other preparations **except**:

i) when included in Schedule 4.

ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules.

B) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

C) not labelled for the treatment of children 6 years of age or less.

D) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin. or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

A) packed in blister or strip packaging or in a container with a child-resistant closure.

B) in a primary pack containing not more than 20 tablets or capsules.

C) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

D) not labelled for the treatment of children 6 years of age or less. and

E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin.

Schedule 3 – Proposed Amendment

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.

2.4 Piracetam

Scheduling proposal

The medicines scheduling delegate has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To reschedule piracetam and its analogues and derivatives from Schedule 4 to unscheduled (exempt).

Substance summary

The applicant has provided the following information regarding Piracetam:

Piracetam acts on the central nervous system (CNS) and has been described as a nootropic; it is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood viscosity at high doses. Piracetam is used as an adjunct in the treatment of myoclonus of cortical origin, and has also been used in dementia. Other disorders or states in which it has been tried (on the basis of a supposed 'cerebrocortical insufficiency' responsive to piracetam) include alcoholism, vertigo, cerebrovascular accidents, dyslexia, behavioural disorders in children, and after trauma or surgery.

In cortical myoclonus, piracetam is given in oral doses of 7.2 g daily, increasing by 4.8 g daily every three or four days up to a maximum of 24 g daily. It is given in two or three divided doses. Once the optimal dose of piracetam has been established, attempts should be made to reduce the dose of other drugs.

Piracetam has been given for various other disorders in a usual oral dose of up to 2.4 g daily in 2 or 3 divided doses; doses of up to 4.8 g daily or higher have been used in severe cases. In severe disorders it has also been given by intramuscular or intravenous injection.

Although piracetam is used in some countries in the management of cognitive impairment and dementia, a systematic (Cochrane) review concluded that the evidence from the published literature did not support this use.

Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness and depression. Other reported adverse effects include gastrointestinal disorders such as abdominal pain, diarrhoea, nausea and vomiting, hypersensitivity reactions, ataxia, vertigo, confusion, hallucinations, angioedema and rashes. Piracetam should not be given to patients with hepatic impairment or with severe renal impairment (creatinine clearance less than 20 mL/minute); dosage reduction is recommended for those with mild to moderate renal impairment. Therapy with piracetam should not be withdrawn abruptly in myoclonic patients due to the risk of inducing seizures. When used to treat cortical myoclonus, piracetam is contraindicated in patients with cerebral haemorrhage, and should be used with caution after major surgery and in those with haemostatic disorders or severe haemorrhage.

Piracetam is rapidly and extensively absorbed from the gastrointestinal tract; peak plasma concentrations are reached within 1.5 hours after oral doses. The plasma half-life is reported to be five hours, and piracetam crosses the blood-brain barrier. Piracetam is excreted almost completely in the urine. It crosses the placenta and is distributed into breast milk.

Scheduling status

Piracetam is currently listed in Schedule 4.

Scheduling history

National Drugs and Poisons Schedule Committee (NDPSC): October 2006

The NDPSC agreed to include piracetam in Schedule 4, on the grounds of harmonisation with New Zealand.

The New Zealand Medicines Classification Committee (MCC) considered the classification of a number of new chemical entities, including piracetam, at its meeting on 17 May 2001. The MCC agreed that, in view of the indications and as it was a new chemical entity, piracetam should be classified as prescription medicine.

Pre-meeting public submissions

Two public submissions were received. These were opposed to the proposal.

They made the following main points:

- Piracetam has been used in dementia or cognitive impairment, but its mechanism of action is not well defined, and evidence for efficacy has not been demonstrated consistently.
- Possible adverse effects of piracetam include insomnia, weight gain, hyperkinesia and depression. Other reported effects include gastrointestinal symptoms (e.g. abdominal pain, diarrhoea), ataxia, confusion, hallucinations, angioedema, confusion, bleeding problems, vertigo and worsening of epilepsy.
- Although the purpose of the current proposal is not clear, the documented characteristics and side effect profile of piracetam would suggest that less restricted availability could pose unacceptable risks to consumers.
- Dietary supplements containing piracetam were the subject of compliance actions by the United States Food and Drug Administration.
- Removing piracetam completely from the poisons schedule could potentially lead to products containing this substance to be sold in a general retail setting (or online) which is not in the interests of public health.
- Piracetam does not have a TGA pregnancy rating but consumers are advised to avoid it during pregnancy due to insufficient data.
- The onus of proof rests with the applicants to show why removing piracetam from the Poisons Standard (thus allowing products containing this substance to be sold in general retail outlets) does not pose a risk to public health.

The public submissions are available at https://www.tga.gov.au/scheduling-delegates-decisions-public-submissions.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of piracetam remains appropriate.

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

The reasons for the recommendation comprised the following:

- Piracetam is not used therapeutically in Australia.
- Its risks outweigh the benefits.
- No Australian data is available on marketing.
- Some of the conditions that piracetam would be used for require medical supervision.
- Piracetam (and its derivatives) is widely marketed as a cognitive enhancement agent. In UK it is prescribed for myoclonus and other off-label conditions. In Switzerland it is prescribed for myoclonus, cognitive disorders and dyslexia. No piracetam containing products are listed on the ARTG.
- Piracetam has low toxicity in short (high-dose) & long-term trials.
- Unexpected effects of the substance may only become evident after widespread use (SPF criteria 8).
- The potential for abuse of Piracetam is low.

- The ailments or symptoms that the substance is used for require medical intervention (SPF criteria 1).
- The experience of the use of the substances under normal clinical conditions is limited (SPF criteria 8).

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors [19];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the current scheduling of piracetam remains appropriate.

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

The reasons for the recommendation comprised the following:

- Piracetam is not used therapeutically in Australia. Risks outweigh the benefits. No Australian data available on marketing. Some of the conditions that piracetam would be used for require medical supervision.
- Piracetam (and its derivatives) is widely marketed as a cognitive enhancement agent. In UK it is prescribed for myoclonus and other off-label conditions. In Switzerland it is prescribed for myoclonus, cognitive disorders and dyslexia. No piracetam containing products are listed on the ARTG.
- Low toxicity in short (high-dose) and long-term trials. Unexpected effects of the substance may only become evident after widespread use (SPF criteria 8).
- Piracetam is not used therapeutically in Australia. Risks outweigh the benefits. No Australian data available on marketing. Some of the conditions that piracetam would be used for require medical supervision.
- Low potential for abuse.
- The ailments or symptoms that the substance is used for require medical intervention (SPF criteria 1).
- The experience of the use of the substances under normal clinical conditions is limited (SPF criteria 8).

[19] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

2.5 Proton pump inhibitors

Scheduling proposal

The medicines scheduling delegate has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- to amend the scheduling of lansoprazole to include oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro oesophageal reflux disease, in packs containing not more than 7 days' supply in Schedule 2.
  - consideration could include whether the scheduling of all the over-the-counter proton pump inhibitors (i.e. esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) should be consistent.
- to amend the scheduling of omeprazole to include oral preparations containing 20 mg or less of omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply in Schedule 2.
  - consideration could include whether the scheduling of all the over-the-counter proton pump inhibitors (i.e. esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) should be consistent.
- to amend the scheduling of rabeprazole to include oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply in Schedule 2.
  - Consideration could include whether the scheduling of all the over-the-counter proton pump inhibitors (i.e. esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) should be consistent.

Substance summary

Esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole are proton pump inhibitor (PPI) medicines. PPIs reversibly reduce gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase proton pump in gastric parietal cells.

PPIs are used in conditions where inhibition of gastric acid secretion may be beneficial, such as the management of peptic ulcer disease, relief of acid-related dyspepsia, treatment of gastro-oesophageal reflux disease (GORD), treatment of NSAID-associated ulceration and treatment of pathological hypersecretory states such as Zollinger-Ellison syndrome.

Over-the-counter (OTC – i.e. Schedule 2 or 3) PPIs are indicated for the relief of heartburn and other symptoms of GORD, when given once daily for at least seven days, and up to 14 days. OTC PPIs appear to have consistent safety and efficacy profiles when used short-term for the relief of symptoms of GORD (OTC use is limited to 14 days except on medical advice, and OTC PPIs are not approved for use in children or adolescents under 18 years of age).

Scheduling status

LANSOPRAZOLE is currently listed in Schedules 3 and 4.

SCHEDULE 3

LANSOPRAZOLE in oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

SCHEDULE 4

LANSOPRAZOLE except when included in Schedule 3.

RABEPRAZOLE is currently listed in Schedules 3 and 4.

SCHEDULE 3

RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

SCHEDULE 4

RABEPRAZOLE except when included in Schedule 3.

PANTOPRAZOLE is currently listed in Schedules 2, 3 and 4.

SCHEDULE 2

PANTOPRAZOLE in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3

PANTOPRAZOLE in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4

PANTOPRAZOLE except when included in Schedule 2 or 3.

ESOMEPRAZOLE is currently listed in Schedules 3 and 4. However, the delegate has proposed, in an October 2015 interim decision, to reschedule esomeprazole, so that it will be listed in Schedules 2, 3 and 4, as follows (with a proposed implementation date of 1 February 2016).

SCHEDULE 2

ESOMEPRAZOLE in oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3

ESOMEPRAZOLE in oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4

ESOMEPRAZOLE except when included in Schedule 2 or 3.

Scheduling history

National Drugs and Poisons Schedule Committee: June 2005

The NDPSC included the PPI, pantoprazole, in Schedule 3, in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply (the NDPSC subsequently amended the implementation date until 1 May 2008).

National Drugs and Poisons Schedule Committee: June 2009

The NDPSC agreed to down-schedule rabeprazole to Schedule 3 in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply (i.e. with pack size and indication restrictions similar to those for pantoprazole).

National Drugs and Poisons Schedule Committee: February 2010

The NDPSC decided to schedule lansoprazole and omeprazole similarly to pantoprazole and rabeprazole, to harmonise with New Zealand.

Advisory Committee on Medicines Scheduling: November 2013

Delegate's decision: March 2014

ACMS considered an application to down-schedule from Schedule 4 to Schedule 3 esomeprazole in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply. ACMS recommended, and the delegate confirmed, that esomeprazole should be down-scheduled to Schedule 3, as requested.

Advisory Committee on Medicines Scheduling: November 2014

Delegate's decision: March 2015

The ACMS recommended, and the delegate confirmed, a new entry in Schedule 2 for pantoprazole when supplied in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days of supply. The implementation date for this decision was 1 June 2015.

Advisory Committee on Medicines Scheduling: July (August) 2015

Delegate's interim decision: October 2015

The ACMS recommended a new entry in Schedule 2 for esomeprazole when supplied in oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days of supply.

The ACMS also proposed that the medicines delegate consider initiating a proposal to create new Schedule 2 entries for lansoprazole, omeprazole and rabeprazole in packs containing not more than 7 days' supply (consistent with the current Schedule 2 entry for pantoprazole, and the proposed Schedule 2 entry for esomeprazole).

The delegate's interim decision supported these ACMS recommendations. The proposed implementation date for the inclusion of esomeprazole in Schedule 2 is 1 February 2016.

Pre-meeting public submissions

One public submission was received which made the following main points:

- Objected to the schedule 2 entries. However, noted because other entries exist, that other entries should be included as well.
- Under these circumstances, the following recommendations were offered:
  - The Schedule 2 entries for PPIs should be consistent. The maximum strength allowable as a Schedule 2 entry should reflect the lowest effective dose.

– Given that consumers will be able to purchase these products without mandatory health professional oversight, a new advisory statement should be mandated that instructs a consumer to seek the advice of a health professional if they are pregnant or breastfeeding.

The public submission is available at https://www.tga.gov.au/scheduling-delegates-decisions-public-submissions.

ACMS advice to the delegate

The ACMS recommended that lansoprazole, omeprazole and rabeprazole be down-scheduled from Schedule 3 to Schedule 2 as follows:

- Lansoprazole in oral preparations containing 15 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply, be down-scheduled from Schedule 3 to Schedule 2.
- Omeprazole in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply, be down-scheduled from Schedule 3 to Schedule 2.
- Rabeprazole in oral preparations containing 10 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply, be down-scheduled from Schedule 3 to Schedule 2.

The ACMS recommended an implementation date of 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- The PPIs are safe and effective first line treatment for consumers with frequent symptoms of GORD.
- Esomeprazole and pantoprazole are already recommended for Schedule 2. The other Schedule 3 PPIs have similar safety and efficacy profiles. Limiting the 7 day availability pack size and lowest effective dose minimises the opportunity for long term adverse effects.
- Very low toxicity with short-term use.
- The proposed Schedule 2 seven (7)-day supply, labelling (including RASML warning statements) and provision of Consumer Medicines Information will promote appropriate use and health education as Schedule 2.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[20];

[20] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

· Other relevant information.

Delegate's interim decision

The delegate's interim decision is to include lansoprazole, omeprazole, rabeprazole in Schedule 2 as proposed below – see "Schedule Entry".

The proposed implementation date is 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

· The PPIs are safe and effective first line treatment for consumers with frequent symptoms of GORD.

· Esomeprazole and pantoprazole are already recommended for Schedule 2. The other Schedule 3 PPIs have similar safety and efficacy profiles. Limiting the 7 day availability pack size and lowest effective dose minimises the opportunity for long term adverse effects.

· Very low toxicity with short-term use.

· The proposed Schedule 2 7-day supply, labelling (including RASML warning statements) and provision of Consumer Medicines Information will promote appropriate use and health education as Schedule 2.

Schedule entry

LANSOPRAZOLE

SCHEDULE 2 – New entry

LANSOPRAZOLE in oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3 – Amendment

LANSOPRAZOLE in oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4 – Amendment

LANSOPRAZOLE except when included in Schedule 2 or 3.

OMEPRAZOLE

SCHEDULE 2 – New entry

OMEPRAZOLE in oral preparations containing 20 mg or less of omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3 – Amendment

OMEPRAZOLE in oral preparations containing 20 mg or less of omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4 – Amendment

OMEPRAZOLE except when included in Schedule 2 or 3.

RABEPRAZOLE

SCHEDULE 2 – New entry

RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3 – Amendment

RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4 – Amendment

RABEPRAZOLE except when included in Schedule 2 or 3.

2.6 Flubromazolam

Scheduling proposal

The medicines scheduling delegate has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To create a new entry for flubromazolam in Schedule 9 (flubromazolam is currently covered by the Schedule 4 entry for benzodiazepine derivatives).

Substance summary

The applicant has provided the following information regarding flubromazolam:

Flubromazolam is a benzodiazepine derivative. It is a triazolo analogue of the designer benzodiazepine, flubromazepam.

Benzodiazepines enhance the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. This results in anxiolytic, sedative, hypnotic, muscle relaxant and antiepileptic effects.

Molecular formula: $C_{17}H_{12}BrFN_4$

CAS Number: 612526-40-6

IUPAC name: 8-bromo-6-(2-fluorphenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a]benzodiazepine.

Flubromazolam has high potency, and can cause strong sedation and amnesia at oral doses as low as 500 micrograms. Flubromazolam has an onset of effect of 30 minutes, and duration of effect of 12-18 hours. After-effects are experienced for ≥ 24 hours. There is a risk of fatal overdose if benzodiazepines such as flubromazolam are combined with other central nervous system depressants such as opioid analgesics, alcohol and 4-hydroxybutanoic acid (GHB).

There is a risk of unintended over-dosing. People who use flubromazolam for its psychoactive properties reported compulsive re-dosing. Abrupt discontinuation of flubromazolam following regular dosing over several days can result in a withdrawal phase that includes rebound symptoms such as increased anxiety and insomnia.

Flubromazolam has recently become available online (products available for sale online include the pure substance and 250 microgram pellets).

Flubromazolam has no currently established therapeutic use and is likely to present a high risk of dependency, abuse, misuse or illicit use. The dangers associated with flubromazolam are such as to warrant limiting use to strictly controlled medical and scientific research. On this basis, flubromazolam meets two of the factors for inclusion in Schedule 9 of the Poisons Standard.

Flubromazolam is a triazolo analogue of the designer benzodiazepine, flubromazepam (7- bromo-5-(2-fluorphenyl)-1,3-dihydro-1,4-benzodiazepine-2-one). Flubromazepam has a much longer time to onset of effect (4 hours) and much longer duration of effect (3 days) than flubromazolam.

Scheduling status

FLUBROMAZOLAM

Flubromazolam is currently not specifically scheduled.

Flubromazolam is a benzodiazepine derivative, and is therefore currently covered by the entries for 'Benzodiazepine derivatives' in Schedule 4 and Appendix D.

SCHEDULE 4

BENZODIAZEPINE derivatives **except** when separately specified in these Schedules.

APPENDIX D

Paragraph 5 – Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription)

BENZODIAZEPINE DERIVATIVES, including those separately specified in Schedule 4 and Schedule 8.

[The additional controls on possession or supply specified in Appendix D only apply to the substances listed when included in Schedule 4 and Schedule 8.]

OTHER BENZODIAZEPINES – Specific schedule entries

Schedule 4 includes specific entries for the following benzodiazepines (in addition to the entry for benzodiazepine derivatives): bromazepam; chlordiazepoxide; clobazam; clonazepam; clorazepate; diazepam; flurazepam; ketazolam; loprazolam; lorazepam; lormetazepam; medazepam; midazolam; motrazepam; nitrazepam; oxazepam; prazepam; quazepam; temazepam; triazolam; zolazepam.

The benzodiazepines, alprazolam and flunitrazepam, are currently listed in Schedule 8.

Currently, there do not appear to be entries for any benzodiazepines in Schedule 9.

Scheduling history

FLUBROMAZOLAM

Flubromazolam has not previously been considered for scheduling.

BENZODIAZEPINES

In May 1982, the general class of benzodiazepines was included in Schedule 4. In May 1986, some individual benzodiazepine substances were listed in Schedule 4 (bromazepam, diazepam). Other individual benzodiazepine substances have subsequently been listed in Schedule 4.

National Drugs and Poisons Schedule Committee (NDPSC): February 1997; May 1997; August 1997; November 1997; February 1998

In February 1997, the NDPSC considered a proposal to include flunitrazepam in Schedule 9, in response to representations from the Chairman of the Australian Health Ministers' Advisory Council (AHMAC). The NDPSC decided that the scheduling of flunitrazepam should be considered in May 1997. In May 1997, the NDPSC foreshadowed a Schedule 8 entry for flunitrazepam, on the basis of its abuse

and the harmful effects associated with abuse. The NDPSC agreed, in August 1997, to defer further consideration until the November 1997 meeting. The NDPSC agreed, in November 1997, that there was an on-going public health issue associated with the abuse and misuse of flunitrazepam, and decided to reschedule it from Schedule 4 to Schedule 8. The NDPSC confirmed this decision in February 1998.

National Drugs and Poisons Schedule Committee (NDPSC): August 1998

The November 1997 NDPSC meeting had decided that a review of the scheduling of benzodiazepines was appropriate, following a decision to include flunitrazepam in Schedule 8, due to its known abuse and public health concerns associated with this abuse. The NDPSC considered the submissions received in response to the decision to undertake the review at its August 1998 meeting, and agreed that it was appropriate that those benzodiazepines currently included in Schedule 4 of the Standard for uniform scheduling of drugs and poisons should remain in Schedule 4.

National Drugs and Poisons Schedule Committee (NDPSC): June 2010

Delegate decision: August 2010

The NDPSC considered the scheduling of alprazolam, following a request that it be rescheduled to Schedule 8, in response to concerns about misuse and abuse. The NDPSC decided that the current scheduling of alprazolam (Schedule 4) remained appropriate. The delegate confirmed this decision in August 2010.

Advisory Committee on Medicines Scheduling (ACMS): March 2013

Delegate decision: June 2013

The ACMS considered a proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8 in March 2013. The ACMS recommended that alprazolam be rescheduled from Schedule 4 to Schedule 8. The ACMS recommended that the current scheduling of other benzodiazepines remained appropriate, and that benzodiazepines should be included in Appendix D, paragraph 5.

Reasons for the recommendation to include alprazolam in Schedule 8 included public health concerns, increased morbidity and mortality in overdose, abuse and misuse (particularly in association with opioids) and evidence of widespread misuse of alprazolam.

The delegate decided to include alprazolam in Schedule 8. The delegate also decided to include a new entry in Appendix D, paragraph 5, for "Benzodiazepine derivatives, including those separately specified in Schedule 4 and Schedule 8".

Pre-meeting public submissions

No public submissions were received.

ACMS advice to the delegate

The ACMS recommended flubromazolam be included in Schedule 9.

The ACMS recommended an implementation date of 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- Currently there are no established therapeutic uses for flubromazolam.

- Flubromazolam is highly potent and causes sedation and amnesia at low doses.
- Flubromazolam has no apparent therapeutic benefit.
- Risks of unintentional overdose and undetected "spiking" due to very low effective dose.
- There are reports of misuse and abuse of flubromazolam in online drug user forums.
- There have been seizures of flubromazolam that was intended for import into South Australia.
- Flubromazolam has no legitimate therapeutic use; used only for illicit recreational use, apparently increasing as advertising and discussed via internet.
- Flubromazolam is similar to other benzodiazepines but very low dosages for effectiveness as well as toxicity.
- There is a risk of fatal overdose if flubromazolam is ingested in combination with other CNS depressants such as alcohol, opioid analgesics and GHB. Users report tolerance and compulsive re-dosing.
- There is a risk of withdrawal effects including increased anxiety and insomnia if flubromazolam is abruptly discontinued.
- Flubromazolam is available online as pure substance or pellets and is sold via the internet as raw material and "pellets" 0.75mg and 1.25mg.
- There is a risk that users will have difficulty accurately measuring the dose of flubromazolam.
- There is a high potential for misuse and abuse of flubromazolam.
- The low effective dose of flubromazolam could be a concern in drug facilitated crimes.
- Unlikely that there ever will be a therapeutic use as safer benzodiazepines would be preferred.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[21];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to include Flubromazolam in Schedule 9.

The proposed implementation date is 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the

[21] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- Currently there are no established therapeutic uses for flubromazolam. It is highly potent and causes sedation and amnesia at low doses. No apparent therapeutic benefit. Risks of unintentional overdose and undetected "spiking" due to very low effective dose
- There are reports of misuse and abuse of flubromazolam in online drug user forums. There have been seizures of flubromazolam that was intended for import into South Australia. No legitimate therapeutic use; used only for illicit recreational use, apparently increasing as advertising and discussed via internet.
- There is a risk of fatal overdose if flubromazolam is ingested in combination with other CNS depressants such as alcohol, opioid analgesics and GHB. Users report tolerance and compulsive re-dosing. There is a risk of withdrawal effects including increased anxiety and insomnia if flubromazolam is abruptly discontinued. Similar to other benzodiazepines but very low dosages for effectiveness as well as toxicity.
- Flubromazolam is available online as pure substance or pellets. There is a risk that users will have difficulty accurately measuring the dose of flubromazolam. There is a risk of unintended over-dosing. Sold via internet as raw material and "pellets" 0.75mg and 1.25mg.
- There is a high potential for misuse and abuse of flubromazolam.
- The low effective dose of flubromazolam could be a concern in drug facilitated crimes. Unlikely that there ever will be a therapeutic use as safer benzodiazepines would be preferred.

Schedule entry

SCHEDULE 9 – New entry

Flubromazolam

2.7 Performance and image enhancing drugs

Scheduling proposal

The medicines scheduling delegate has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

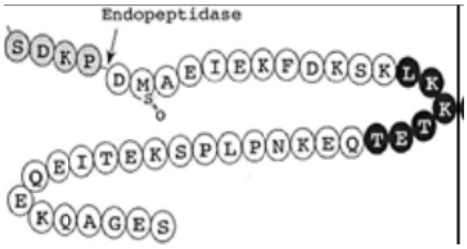
- To create new Schedule 4 and Appendix D, Item 5 entries for Thymosin Beta 4 and TB-500 to control the manner in which they are advertised, sold and accessed without legitimate purpose.

Substance summary

The applicant has provided the following information regarding Performance and image enhancing drugs:

Thymosin Beta 4 and TB-500

Thymosin Beta 4 (Thymosin β4) is a growth factor affecting muscle, tendon or ligament, vascularisation and regenerative capacity. Thymosin Beta 4 is a 43 amino acid peptide – the molecular structure is shown in the diagram below where each letter indicates one of the 20 different amino acids.



TB-500 is a short peptide analogue of Thymosin Beta 4. TB-500 is presumed by design to have the same properties as Thymosin Beta 4.

These substances are currently used illicitly to enhance sporting performance and more broadly across the community often for body building and image enhancement purposes. The substances are banned by the World Anti-Doping Agency (WADA Prohibited List, 2015) for use by athletes, both in and out of competition.

Fibroblast Growth Factors

Fibroblast Growth Factors (FGFs) are a family of growth factors involved in angiogenesis, wound healing, embryonic development and various endocrine signalling pathways. FGFs also have a role in the processes of proliferation and differentiation of wide variety of cells and tissues (Thisse & Thisse, 2005; Turner & Grose, 2010).

Scheduling status

Thymosin Beta 4, Tb-500 and Fibroblast Growth Factors are currently not listed in the schedules or appendices in the Standard for uniform scheduling of medicines and poisons (SUSMP).

Scheduling history

Advisory Committee on Medicines Scheduling: November 2015

Delegate's decision: March 2015

The ACMS considered a proposal to include new entries in Schedule 4 and Appendix D for a number of performance and image enhancing drugs. The ACMS recommended, and the delegate confirmed, that the following substances should be included in Schedule 4 and in Appendix D, Item 5 [Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription)]:

- growth hormone releasing hormones (GHRHS)
- growth hormone secretagogues (GHSS)
- growth hormone releasing peptides (GHRPS)

The ACMS recommended similarly for new individual substance entries for:

- CJC-1295 (CAS No. 863288-34-0)
- ipamorelin
- pralmorelin (growth hormone releasing peptide-2) (GHRP-2)
- growth hormone releasing peptide-6 (GHRP-6)
- hexarelin
- Aod-9604 (CAS No. 221231-10-3).

Pre-meeting public submissions

No public submissions were received.

ACMS advice to the delegate

The ACMS recommended that:

- Thymosin Beta 4, TB-500 and Fibroblast Growth Factors are included in Schedule 4 and in Appendix D, Item 5.
- Thymosin Beta 4, TB-500 and Fibroblast Growth Factors are listed in Appendix D, Part 5.

The ACMS recommended an implementation date of 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- There is limited research regarding the harms and possible therapeutic benefits of these substances.
- No form of Thymosin Beta 4 is yet approved for human therapeutic use anywhere in the world.
- The medications are considered experimental in humans, with potential side effects including carcinogenicity and cardiovascular problems.
- The substances are used as a performance or image enhancing agent.
- Toxicity is unknown due to the experimental nature of the medications.
- Misuse/abuse of Fibroblast Growth Factors have the potential to cause adverse health effects like cancer, cardiovascular problems & endocrinological health outcomes.
- The products have not been approved for use in Australia, and as such this section is unregulated.
- There is potential for abuse given that the substances are used as a performance or image enhancing agent.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[22];
- Other relevant information.

[22] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Delegate's interim decision

The delegate's interim decision is to include Thymosin Beta 4, TB-500 and Fibroblast Growth Factors in Schedule 4 and Appendix D item as per the below proposed wording for the schedule entries.

The proposed implementation date is 1 June 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 the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- There is limited research regarding the harms and possible therapeutic benefits of these substances.
- No form of thymosin beta-4 is yet approved for human therapeutic use anywhere in the world.
- The medications are considered experimental in humans, with potential side effects including carcinogenicity and cardiovascular problems.
- Used as a performance or image enhancing agent.
- Unknown due to the experimental nature of the medications.
- Misuse / abuse of Fibroblast Growth Factors have potential to cause adverse health effects like cancer, cardiovascular problems and endocrinological health outcomes.

Schedule entry

Schedule 4 – New entries

Thymosin Beta 4 (Thymosin β4)

TB-500

Fibroblast Growth Factors

Appendix D, Item 5 – New entries