Australian Government
Department of Health
Therapeutic Goods Administration

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

June 2016

(ACCS, ACMS and Joint ACCS-ACMS meetings – March 2016)

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

The delegates of the Secretary to the Department of Health hereby give notice of delegates' final decisions for amending the *Poisons Standard* (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* - SUSMP) under subsections 42ZCZS and 42ZCZX the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (implementation date) of the decision.

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the March 2016 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#16);
- scheduling proposals initially referred to the March 2016 meeting of the Advisory Committee on Medicines Scheduling (ACMS#17);
- scheduling proposals initially referred to the March 2016 Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS#12); and
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 11 November 2015 and 10 December 2015 on the TGA website at: Public notice about scheduling.

Edited versions of public submissions received in response the invitation were published on 12 May 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

The delegates' interim decisions on recommendations by the ACCS#16, ACCS-ACMS#12 and ACMS#17 were published on 12 May 2016 at Reasons for Delegate's interim decisions and invitation for further comment. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions.

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

Edited versions of valid public submissions received in response to the interim decisions will be published at Public submissions on scheduling matters.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either confirming, varying or setting aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2015), available at SPF, February 2015.

Publishing of the amendments to the Poisons Standard

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

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	
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

Contents

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

1. Scheduling proposals referred to the March 2016 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#16)

Summary of delegate's final decisions

Substance	Final Decision
Crystal violet and related dyes	**Schedule 10 - New Entry** METHYLROSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) and the following TRIARYLMETHANE DYES– for use in hair dyes: – Acid Violet 49 (CAS No. 1694-09-3), – Ethyl Violet (CAS No. 2390-59-2), – Basic Blue 7 (CAS No. 2390-60-5), – Basic Blue 26 (CI 44045) (CAS No. 2580-56-5). **Schedule 6 - New Entries** METHYLROSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) and the following TRIARYLMETHANE DYES: – Acid Violet 49 (CAS No. 1694-09-3), – Ethyl Violet (CAS No. 2390-59-2), – Basic Blue 7 (CAS No. 2390-60-5), – Methylium, 4-(dimethylamino)phenylbis4-(ethylamino)-3-methylphenyl-, acetate (CAS No. 72102-55-7), **except** when included in Schedule 4 or 10. BASIC BLUE 26 (CAS No. 2580-56-5) **except** when used as a colourant in cosmetics not intended to be in contact with mucous membranes. **Index Entries:** Crystal violet - see methylrosanilinium chloride Gentian violet - see methylrosanilinium chloride Implementation date: 1 October 2016.

Substance	Final Decision
Disperse yellow 3	**Schedule 10 - New Entry** DISPERSE YELLOW 3 - for use in hair dyes. **Schedule 6 - New Entry** DISPERSE YELLOW 3 **except** when in Schedule 10. **Appendix E, Part 2 - New Entry** DISPERSE YELLOW 3. Standard statements: A, S1. **Appendix F, Part 3 - New Entry** DISPERSE YELLOW 3. Warning Statement: 28. Safety direction: 4. Implementation date: 1 October 2016.
Chrysoidine base	**Schedule 6 - New Entry** CHRYSOIDINE **except** when in Schedule 10. **Schedule 10 - New Entry** CHRYSOIDINE in preparations for use in hair dyes. **Appendix E, Part 3 - New entry** CHRYSOIDINE. Standard statements: A, S1, E1. Implementation date: 1 October 2016.
p-Aminophenol	**Schedule 6 - New Entry** p-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of p-aminophenol 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.

Substance	Final Decision
	Appendix E, Part 2 - New Entry p-AMINOPHENOL. Standard statements: A, S1. **Appendix F, Part 3 - New Entry** p-AMINOPHENOL. Warning Statement: 28. Implementation date: 1 June 2017.
2-Methylresorcinol	**Schedule 6 - New Entry** 2-METHYLRESORCINOL **except**: a) in non-oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - 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 1.8 per cent or less of 2-methylresorcinol 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 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, Part 2 - New Entry** 2-METHYLRESORCINOL. Standard statements: A, E1. **Appendix F, Part 3 - New Entry** 2-ME Safety direction: 1.THYLRESORCINOL. Safety direction: 1. Implementation date: 1 June 2017.

Substance	Final Decision
2,4-Diamino-5-methylphenetole	**Index - New Entry** 2,4-DIAMINO-5-METHYLPHENETOLE cross reference: PHENYLENEDIAMINES Implementation date: 1 October 2016.
2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine	**Index - New Entry** 2-CHLORO-5-NITRO-*N*-HYDROXYETHYL-*p*-PHENYLENEDIAMINE cross reference: PHENYLENEDIAMINES Implementation date: 1 October 2016.
Bis-Isobutyl PEG/PPG-20/35/Amodimethicone Copolymer	***Final decision has been deferred.***
Propamocarb	Current listing of PROPAMOCARB (Schedule 5) remains appropriate.
Fluopicolide	**Appendix B, Part 3 - New Entry** FLUOPICOLIDE. Part 1 - Reasons for Entry - a) low toxicity. Part 2 - Area of Use - 1.3. Implementation date: 1 October 2016.
Nonanoic acid (NNA)	**Schedule 5 - New Entry** NONANOIC ACID **except** in preparations containing 10 per cent or less of nonanoic acid Implementation date: 1 February 2017.
Di-Bak Parkinsonia	**Schedule 5 - New Entries** LASIODIPLODIA PSEUDOTHEOBROMAE **except** when used as a herbicide in capsule preparations at a concentration of 16 CFU or less per capsule. NEOSCYTALIDIUM NOVAEHOLLANDIAE **except** when used as a herbicide in capsule preparations at a concentration of 16 CFU or less per capsule. MACROPHOMINA PHASEOLINA **except** when used as a herbicide in capsule preparations at a concentration of 16 CFU or less per capsule. Implementation date: 1 October 2016.

Substance	Final Decision
Streptomyces lydicus WYEC 108	**Appendix B, Part 3 - New Entry** STREPTOMYCES LYDICUS WYEC 108 Part 1 - Reasons for Entry - a) low toxicity. Part 2 - Area of Use - 1.3 - Fungicide. Implementation date: 1 October 2016.
Isopyrazam	**Schedule 6 - New Entry** ISOPYRAZAM. Implementation date: 1 October 2016.
4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone	***Final decision has been deferred.***
Methyldibromo glutaronitrile sodium	**Schedule 6 - Amend Entry** METHYLDIBROMO GLUTARONITRILE **except** when in Schedule 10. **Schedule 10 - Amend Entry** METHYLDIBROMO GLUTARONITRILE in preparations intended to be in contact with the skin, including cosmetic use. Implementation date: 1 October 2016.
Potassium hydroxide and sodium hydroxide	**Schedule 6 - Amend Entry** POTASSIUM HYDROXIDE (excluding its salts and derivatives) **except**: a) when included in Schedule 5 or 10; or b) in preparations containing 5 per cent or less of potassium hydroxide being: i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or ii) liquid or semi-solid preparations, the pH of which is 11.5 or less; or SODIUM HYDROXIDE (excluding its salts and derivatives) **except**: a) when included in Schedule 5 or 10; or b) in preparations containing 5 per cent or less of sodium hydroxide being: i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or ii) liquid or semi-solid preparations, the pH of which is 11.5 or less. Implementation date: 1 October 2016.

1.1 Crystal violet and related dyes

Referred Delegate's Scheduling proposal

- To create a new group Schedule 6 entry for Crystal violet (methylrosanilinium chloride) and related dyes to regulate their use in hair dye products and to provide appropriate exemptions.

Applicant's application and scheduling proposal

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

- To create a new group Schedule 6 entry for Crystal violet (methylrosanilinium chloride) and related dyes to regulate their use in hair dye products and to provide appropriate exemptions.

The reasons for the request are:

- Appropriate scheduling and labelling should be undertaken to preclude the use of crystal violet and related dyes in hair dye products. Crystal violet is already listed in Schedule 4 of the SUSMP. Due to the similarities in their toxicity profiles, the dyes related to crystal violet (CAS Nos: 1694-09-3; 2390-59-2; 2390-60-5; 2580-56-5 and 72102-55-7) should also be restricted from use in hair dye products. These chemicals also have industrial uses which should be appropriately controlled provided that the IMAP worker health and safety recommendations are implemented.
- The chemicals are suspected of being carcinogenic. Whilst data are limited for some of the chemicals in the group, crystal violet (CAS No. 548-62-9) and benzyl violet (CAS No. 1694-09-3) are classified as having 'Limited evidence of carcinogenic effect'.
- The chemicals are acutely toxic and cause serious eye damage; and
- The chemicals, basic blue 7 (CAS No. 2390-60-5) and C.I. basic blue 26 (CAS No. 2580-56-5) have reported cosmetic use in hair dyes in Australia.

Substance summary

The chemicals in this group are synthetic organic compounds, used extensively as colourants in various applications. They are chemically similar in that they all possess a triarylmethane backbone with similar chemical chromophores without any clear toxicological differences. For matters relating to scheduling and classification, the chemicals could be considered as chemical class or group.

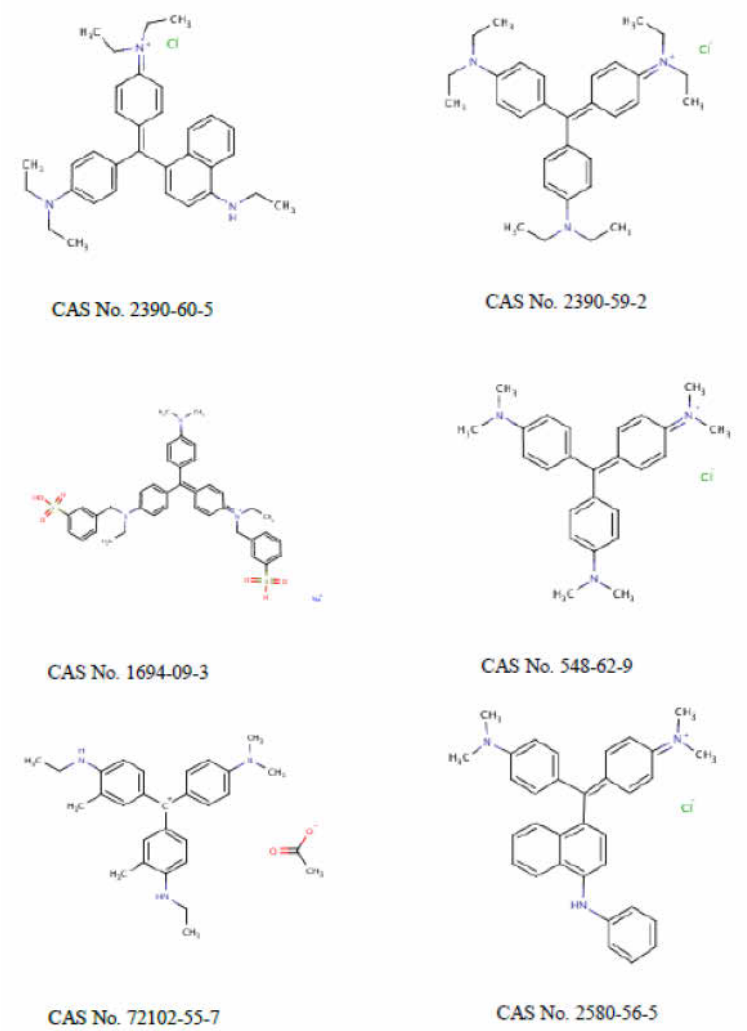

Figure 1: Chemical structures

The toxicity end-points for Crystal violet and related dyes are summarised in the table below.

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bodyweight (bw))	Rat	Ranging from 90-650	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	Human	Limited, unreliable data	-
Eye irritation	Rabbit	Severe irritant	Schedule 6
Skin sensitisation	N/A	No data	-

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

Acute toxicity

Crystal violet was found to have moderate to high acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD_{50}) in rats ranges from 90 mg/kg bw to 650 mg/kg bw for chemicals in this group. Data on ethyl violet indicate similar toxicity. As the chemicals in this group are close analogues of crystal violet or ethyl violet, the classification should apply to all the members of this group.

Skin irritation

No reliable data are available for the chemicals in this group.

Eye irritation

Crystal violet is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). The available data support this classification. In eye irritation studies, crystal violet caused serious eye damage and the effects were not reversible within the observation periods. The other chemicals in this group are likely to have similar irritation effects.

Sensitisation

No data are available.

Repeat-dose toxicity

Studies suggest that the chemicals in this group do not represent a significant concern for repeated dose toxicity. Crystal violet was assessed for carcinogenicity in B6C3F1 mice in a life-time dosing study.

Genotoxicity and mutagenicity

Positive results were reported for crystal violet in two *in vitro* point mutation assays (Ames test) in *Salmonella typhimurium* strains TA 98, TA 1535 and TA 1538, with or without metabolic activation. Positive results were also observed in several other *in vitro* assays conducted with the chemical. However, while there is a concern for mutagenicity, in the absence of clear positive *in vivo* data, the available data are insufficient to conclude that these chemicals are genotoxic.

Carcinogenicity

The chemicals, crystal violet (CAS No. 548-62-9) and benzyl violet (CAS No. 1694-09-3) are classified as hazardous—Category 3 carcinogenic substance—with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40) in the HSIS (Safe Work Australia). The available data support this classification and an extension of this classification to the other chemicals in the group.

Crystal violet was assessed for carcinogenicity in B6C3F1 mice in a life-time dosing study. Mice (150 mice/sex/dose) were dosed with the chemical by dietary administration at 0, 100, 300 or 600 ppm (equivalent to 0, 5, 15 or 30 mg/kg bw/day). Hepatocellular adenomas and carcinomas were the most common lesions, with significant dose-related increases found at 24 months in males and at both 18 and 24 months in females. The females also showed statistically significant dose-related increases in adenoma of the Harderian gland and in type A reticulum cell sarcoma in the urinary bladder, uterus, ovaries and vagina. Under these test conditions, the chemical was found to be carcinogenic in mice in several different organs.

Reproduction and developmental toxicity

In a reproduction study, male and female weanling rats were dosed with crystal violet at 0, 100, 300 or 600 ppm in diet for 80 days. During dosing, females and males from the same dose level were mated. Two males and two females were selected from each litter at random (F1a generation). The F1a pups continued on the same dose levels as their respective parents. In total, 570 male and 570 female F1a rats were fed crystal violet 0, 100, 300 or 600 ppm diet (equal to approximately 0, 30/40, 8/1000 or

160/200 mg/kg bw/day for males/females, respectively) for 24 months. Food consumption, body weights and clinical signs were recorded weekly. Complete necropsy, histopathological examination and clinical chemistry analysis were performed on selected animals at 12, 18 and 24 months. The majority of neoplastic lesions were observed only at the 24-month necropsy. Increases in the incidence of follicular cell adenocarcinomas of the thyroid were statistically significant in males in the highest dose group, and in females in the two highest dose groups. Hepatocellular adenomas were significantly increased at 24 months in males in the 300 ppm and 600 ppm feed groups.

Observation in humans

There are limited data indicating that crystal violet causes mild skin irritation in humans; however, very few experimental details were provided.

Public exposure

The chemicals, C.I. basic blue 7 (CAS No. 2390-60-5) and C.I. basic blue 26 (CAS No. 2580-56-5) have reported cosmetic use in hair colourant formulations in Australia.

The chemicals have reported cosmetic use as hair colourants overseas (CAS No. 548-62-9; CAS No. 2390-59-2; CAS No. 2580-56-5; CAS No. 2390-60-5).

International regulations

The chemicals are listed on the following:

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products (CAS No. 548-62-9; CAS No. 1694-09-3; CAS No. 2390-59-2; CAS No. 2390-60-5; CAS No. 2580-56-5);
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain (CAS No. 548-62-9; CAS No. 1694-09-3; CAS No. 2580-56-5);
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist') (CAS No. 548-62-9; CAS No. 1694-09-3; CAS No. 2390-59-2; CAS No. 2390-60-5; CAS No. 2580-56-5); and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products (CAS No. 548-62-9; CAS No. 1694-09-3; CAS No. 2580-56-5).

The chemicals (CAS No. 548-62-9; CAS No. 2580-56-5) are listed on the candidate list of substances of very high concern for eventual inclusion in Annex XIV (ECHA, 2014). In the EU, companies could have legal obligations if the chemical that they produce, supply or use is included on the candidate list whether on its own, in mixtures, or present in articles.

Scheduling status

The chemical crystal violet (CAS No. 548-62-9) is listed in schedule 4 as follows:

Schedule 4

CRYSTAL VIOLET for human use **except** when used as a dermal marker.

No other chemicals in this group are listed in the Poisons Schedule.

Scheduling history

Crystal violet was included in Schedule 4 in August 1989. The Committee noted the opinion of ADEC that crystal violet is a carcinogen and should not be available for use in humans. The Committee determined that crystal violet may be used as a surgical marker, as it did not present a long term

hazard, but its use as a marker on the skins of food-producing animals may present a public health risk.

Pre-meeting public submissions

Two public submissions were received. The first submission noted that Crystal Violet is used in topical antiseptic products and is entered in the ARTG as a 1% topical antiseptic solution and therefore therapeutic goods should be exempted from any proposed Schedule 6 entry for Crystal Violet.

The second submission did not object to aligning scheduling controls with those in the European Union, but questioned whether this could be achieved in a single schedule entry. They noted four of the six CAS numbers in the NICNAS IMAP list are on the EU Cosmetics Regulations Annex II (i.e. banned from cosmetic use): 548-62-9, 1694-09-3, 2390-59-2 and 2390-60-5. They had no objections to these being added to Schedule 10, similar to the Benzidine-based azo-dyes schedule entry. They further noted one substance in the IMAP list, CI 44045 (CAS number 2580-56-5) is listed in EU Cosmetics Regulations Annex IV, colourants allowed in cosmetics, with a restriction that it is not to be used in products applied to mucous membranes, and not allowed in hair dyes. They believe schedule entry for this one should allow continued use in cosmetics, except hair dyes and products which contact with mucous membranes. They also stated that for the substance CAS number 72102-55-7, no information on use in cosmetics or any restrictions in consumer products was available, but that it may be used in newsprints, and scheduling controls therefore should focus on this specific use.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

The Committee advised a new Schedule 10 entry for methylrosanilinium chloride (crystal violet) and specified related dyes for use in hair dyes, as well as a new Schedule 6 entry for other uses of related dyes. Members also advised a separate entry for the dye Basic Blue 26 except when used as a colourant in cosmetics not intended to be in contact with mucous membranes or when, in Schedule 4 or used as a dermal marker.

Members advised the Delegate to consider the appropriate chemical name for the schedule entry and conventions for listing of CAS numbers in the Standard, and to have regard to the implementation date and reasons given for benzidine-based dyes considered previously which have similar safety concerns.

Reasons given by the Committee for the advice were: b) to prevent use in cosmetics and in hair dyes; c) acutely toxic, strong eye irritant with potential for eye damage, consistent with S6; f) alignment with EU restrictions. The chemical name is consistent with that used internationally.

The committee advised the following amendments to the Poisons Standard:

Schedule 10 – New Entry

METHYLROSANILINIUM CHLORIDE AND THE FOLLOWING TRIARYLMETHANE DYES– for use in hair dyes:

- Crystal Violet (CAS No. 548-62-9)
- Acid Violet 49 (CAS No. 1694-09-3)
- Ethyl Violet (CAS No. 2390-59-2)
- Basic Blue 7 (CAS No. 2390-60-5)
- Basic Blue 26 (CI 44045) (CAS No. 2580-56-5)

Schedule 6 – New Entries

METHYLROSANILINIUM CHLORIDE AND THE FOLLOWING TRIARYLMETHANE DYES:

- Crystal Violet (CAS No. 548-62-9)
- Acid Violet 49 (CAS No. 1694-09-3)
- Ethyl Violet (CAS No. 2390-59-2)
- Basic Blue 7 (CAS No. 2390-60-5)
- Methylium, 4-(dimethylamino)phenylbis4-(ethylamino)-3-methylphenyl-, acetate (CAS No. 72102-55-7)

except when in Schedule 4 or when used as a dermal marker.

BASIC BLUE 26 (CAS No. 2580-56-5) **except** when used as a colourant in cosmetics not intended to be in contact with mucous membranes or when in Schedule 4 or when used as a dermal marker.

Schedule 4 – Amend Entry

CRYSTAL VIOLET for human use **except** when used as a dermal marker. – replace "CRYSTAL VIOLET" with "METHYLROSANILINIUM CHLORIDE"

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate notes, and accepts, the advice of the ACCS to create new listings for crystal violet and related triarylmethane dyes in Schedules 6 and 10. The listings are to be made under the name methylrosanilinium chloride, in accordance with an agreement to standardise entries in the Poisons Standard in line with the International Harmonisation of Ingredient Names. The former common names crystal violet and gentian violet are to be cross-referenced in the Index, and for further clarity, the Schedule 6 and 10 entries will include CAS numbers of the specific triarylmethane dyes captured by the entries. A consequent amendment to the current Schedule 4 entry for crystal violet adopts the new nomenclature.

The purpose of the Schedule 10 entry is to restrict use in hair dyes preparations, in alignment with similar restrictions in international cosmetics regulations (EU, NZ, Canada and ASEAN). The toxicological basis for this restriction is the acute toxicity profile, including strong skin irritancy potential. The Schedule 10 entry also captures three related triarylmethane dyes with similar toxicological potential. For all other uses (except human therapeutic use covered under the existing Schedule 4 entry), the substances are listed under a new entry in Schedule 6. A further separate entry in Schedule 6 has been created for Basic Blue 26 (CAS No. 2580-56-5) to align with international

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

regulations, where restrictions on cosmetic use only apply to preparations applied directly to mucous membranes. There was insufficient information, and no recommendation from the ACCS, for the delegate to consider any low concentration exemptions from the proposed entries.

The delegate notes the industry submission that draws attention to the potential human use of gentian violet as a topical antiseptic. However, this use is covered by the existing Schedule 4 entry, which is only changed in relation to the listing name used.

The proposed implementation date is 1 October 2016. An early implementation date is proposed in order to bring the regulation of these ingredients in cosmetic sold in Australia into alignment with international regulations.

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

Schedule 10 – New Entry

METHYLROSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) and the following TRIARYLMETHANE DYES– for use in hair dyes:

- Acid Violet 49 (CAS No. 1694-09-3)
- Ethyl Violet (CAS No. 2390-59-2)
- Basic Blue 7 (CAS No. 2390-60-5)
- Basic Blue 26 (CI 44045) (CAS No. 2580-56-5)

Schedule 6 – New Entries

METHYLROSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) and the following TRIARYLMETHANE DYES:

- Acid Violet 49 (CAS No. 1694-09-3)
- Ethyl Violet (CAS No. 2390-59-2)
- Basic Blue 7 (CAS No. 2390-60-5)
- Methylium, 4-(dimethylamino)phenylbis4-(ethylamino)-3-methylphenyl-, acetate (CAS No. 72102-55-7)

except when included in Schedule 4 or 10.

BASIC BLUE 26 (CAS No. 2580-56-5) **except** when used as a colourant in cosmetics not intended to be in contact with mucous membranes.

Schedule 4 – Amend Entry

CRYSTAL VIOLET for human use **except** when used as a dermal marker. – replace "CRYSTAL VIOLET" with "METHYLROSANILINIUM CHLORIDE"

Index Entries:

Crystal violet – see methylrosanilinium chloride

Gentian violet – see methylrosanilinium chloride

Public submissions on the interim decision

One submission was received. The submission supported the proposal but suggested adding the words "excluding salts and derivatives" to the proposed schedule entries to ensure no other substances are inadvertently captured.

Delegate's final decision

The delegate notes the submission that essentially supports the interim decision, although requesting the addition of words "excluding salts and derivatives" to the proposed entries. No evidence was presented to show that any salts or derivatives would be inadvertently captured by the proposed entries, or that the toxicological profiles of any such salts or derivatives would be sufficiently different from the listed chemicals. Accordingly, the delegate has confirmed the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The implementation date is 1 October 2016.

1.2 Disperse Yellow 3

Referred Delegate's scheduling proposal

- To create a new Schedule 6, 7 or 10 entry for Disperse Yellow 3 to regulate its use in hair dyes and other products.

Applicant's application and scheduling proposal

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

- Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in cosmetic products. Due to the toxicity profile, this chemical should be considered for listing in Schedule 6 of the SUSMP.

The reasons for the request are:

- although use in cosmetic products in Australia is not known, the chemical has identified use in hair dye products. This use is now prohibited in some countries overseas.
- currently, there are no restrictions in Australia on using this chemical in cosmetics. In the absence of any regulatory controls in Australia, the characterised critical health effects, including sensitisation and carcinogenicity, have the potential to pose an unreasonable risk if the chemical is used in hair dye products in Australia.
- the chemical is a known sensitiser which has elicited positive reactions in patch tests at concentrations of 0.01%;
- the chemical is carcinogenic in animals with evidence of a genotoxic mode of action; and
- the NICNAS IMAP Tier II Human Health Report.

Substance summary

Please refer to the NICNAS assessment report for acetamide, N-[4-[(2-hydroxy-5-methylphenyl)azo]phenyl]-.

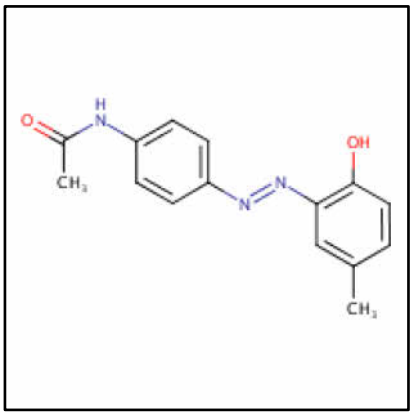

Figure 2. Structure of Disperse Yellow 3

Acute toxicity

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

Toxicity	Species	Disperse Yellow 3	SPF* Classification
Acute oral toxicity LD_{50}	Rat	> 5000 mg/kg bw	Not classified
Skin sensitisation - LLNA challenge and loose-fit coculture-based sensitisation assay (LCSA))		positive	Schedule 6

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

Skin sensitisation

This chemical is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the Hazardous Substance Information System (HSIS) (Safe Work Australia). The positive results reported in a modified LLNA in mice and skin patch tests in humans (see Observation in humans section) support this classification.

The standard and modified (sensitisation—challenge) LLNA were used to test the sensitising potential of Disperse Yellow 3 and its aromatic amine metabolites, 4-Aminoacetanilide and 2-amino-p-cresol (Stahlmann et al., 2006). In the standard LLNA Disperse Yellow 3 and 4-aminoacetanilide were negative, but 2-amino-p-cresol showed a clear positive reaction. However, when the protocol was modified to a sensitisation—challenge assay, all three chemicals produced sensitisation reactions.

Compared with controls, significant increases in lymph node weights, cellularity and in the number of lymphocytes carrying A1 epitopes were observed in animals exposed to Disperse Yellow 3 (10 % and 30 % concentration) and 4-aminoacetanilide (30 % concentration). These results indicated sensitisation reactions. However, stronger sensitisation was induced by 2-amino-p-cresol.

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, the chemical is considered to be genotoxic.

A number of *in vitro* genotoxicity tests gave positive results, and Disperse Yellow 3 also induced DNA damage *in vivo*. The aromatic amine metabolites are also genotoxic *in vivo* and/or *in vitro*.

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40 in the HSIS (Safe Work Australia)). The available data support this classification.

In long-term feeding studies (103 weeks) exposure to the chemical caused tumours in male Fischer (F344) rats and male and female B6C3F1 mice. The liver was the main target organ of carcinogenicity in male rats. In these animals, dose-dependent significant increases in hepatocellular adenomas and combined hepatocellular adenomas and carcinomas were observed in treated males (dose). In addition, combined rare adenoma, mucinous adenocarcinoma and sarcoma, and combined squamous cell papilloma and fibrosarcoma were also identified in the glandular and non-glandular portions of the stomach of the exposed male rats. No tumours were reported in exposed female rats.

There is a lack of epidemiological data to indicate specific links between occupational exposure to the chemical and tumour development.

The mechanism of action underlying the chemical's carcinogenic potential is not fully understood. However, the available data suggest a genotoxic mode of action.

Reproduction and developmental toxicity

No data are available.

Observation in humans

A number of reports indicate sensitisation potential of the chemical. Allergic, contact-type dermatitis was reported in individuals with exposure to textiles coloured with dyes containing Disperse Yellow 3 (IARC, 1990; HSDB). The chemical has been identified as a disperse dye known to cause occupational contact allergic dermatitis in the textile industry (Office of Environmental Health Hazard Assessments, OEHHA, 2012).

Epicutaneous testing of the chemical (1% in petroleum) was conducted in 12 eczema patients with suspected contact allergy to textile dyes. The result showed that five patients had positive reactions to the chemical (Cosmetic Ingredient Review, CIR, 1996).

In another study, a number of patients who tested positive for Disperse Yellow 3 were also positive for the aromatic amine metabolites 4-aminoacetanilide and 2-amino-p-cresol. In this study, 6/10 patients tested with a dilution series of the chemical showed positive reactions. In addition, four patients showed positive reactions at 0.01 % of the chemical. These patients also showed a positive reaction to 4-aminoacetanilide (3/6) and 2-amino-p-cresol (6/6) (Malinauskiene et al., 2012).

Positive results in a patch test performed with a purified form of the dye indicated that it is the chemical and not the impurities that is responsible for the sensitisation response (CIR, 1996).

In a recent review on contact dermatitis from textiles, Malinauskiene et al. (2013) reported that a considerable number of patients showed positive patch test reactions to Disperse Yellow 3 (1 % in petrolatum). Positive responses were seen in approximately 7 % (averaged over 18 studies) of patients suspected or thought likely to have contact dermatitis caused by disperse dye allergy (aimed patch testing). In routine patch testing that included textile dyes (screening testing), a 0.8 % prevalence rate for Disperse Yellow 3 was reported (averaged over 12 studies). In Italy, Disperse Yellow 3 was also found to be one of the prevalent contact allergens in children (Malinauskiene et al., 2013).

Public exposure

No specific Australian use, import or manufacturing information has been identified.

The chemical has reported cosmetic use in oxidative hair dyes. No information is available on the concentrations used. Use of the chemical in cosmetics in the United States of America (USA) was reported in 1992, but there was no documented use in 2011 (Personal Care Product Council, 2011).

International regulations

The chemical is 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 Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

The chemical is also in the EU's list of 179 substances banned for use in hair dye products (European Commission, 2010).

Current scheduling status

Disperse Yellow 3 is not specifically scheduled.

Scheduling history

Disperse Yellow 3 has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. The submission did not object to aligning the scheduling controls for this substance with the EU. They noted Disperse Yellow 3 is listed in Annex II of the EU Cosmetics Regulations and cannot be used in cosmetics in the EU.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

In relation to the Delegate's questions the committee agreed that the sensitisation and carcinogenic potential warrants control in cosmetic and consumer products and should not be used in hair dyes. The committee agreed it was appropriate to have both a Schedule 6 entry for disperse yellow 3 for general use and a Schedule 10 entry to specifically prohibit use in hair dyes, noting the schedule 6 entry effectively prohibits use in cosmetics. Members further agreed that appropriate warning statements for general use to advise of the skin sensitization potential was warranted. The committee advised that the name Disperse Yellow 3 be used in any Schedule entry with a cross-reference to the chemical name 4-(2-hydroxy-5-methylphenylazo)acetanilide in the index. Members agreed that the substance is not captured by the existing benzidine azo dye entries or azo dyes derivatised by diazotisation and therefore should be listed separately in the Standard.

The committee agreed on the following amendments to the Poisons Standard:

Schedule 10 – New Entry

DISPERSE YELLOW 3 – for use in hair dyes.

Schedule 6 – New Entry

DISPERSE YELLOW 3- **except** when in Schedule 10.

Appendix E, Part 2 – New Entry

DISPERSE YELLOW 3.

Standard statements: A, S1.

Appendix F, Part 3 – New Entry

DISPERSE YELLOW 3.

Warning Statement: 28.

Safety direction: 4.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: b) to prevent its use in hair dyes but allow use in other dye situations (e.g. fabrics); and c) toxicity – skin sensitization consistent with Schedule 6 listing.

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 notes and accepts, the advice of the ACCS to create new listings for Disperse Yellow 3 in Schedules 6 and 10, and in Appendices E and F. The listings are to be made under the name Disperse Yellow 3, with the chemical name 4-(2-hydroxy-5-methylphenylazo)acetanilide, cross-referenced in the index. The delegate notes that this substance would not be captured under any existing Schedule entries for phenylenediamines or azo dyes.

The purpose of the Schedule 10 entry is to restrict use in hair dyes preparations, in alignment with similar restrictions in international cosmetics regulations (EU, NZ and ASEAN). The toxicological basis for this restriction is the acute toxicity profile, including skin sensitisation potential shown in both toxicological testing and in human studies. For use in products other than hair dyes, the listings in Schedule 6 and Appendices E and F should provide suitable warnings to product users, including the requirement for the signal heading POISON on product labels. There was insufficient information, and no recommendation from the ACCS, for the delegate to consider any low concentration exemptions from the proposed entries.

The proposed implementation date is **1 October 2016**. An early implementation date is proposed in order to bring the regulation of this oxidative hair dye ingredient in products sold in Australia into alignment with international regulations.

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

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

Schedule 10 – New Entry

DISPERSE YELLOW 3 – for use in hair dyes.

Schedule 6 – New Entry

DISPERSE YELLOW 3- **except** when in Schedule 10.

Appendix E, Part 2 – New Entry

DISPERSE YELLOW 3.

Standard statements: A, S1.

Appendix F, Part 3 – New Entry

DISPERSE YELLOW 3.

Warning Statement: 28.

Safety direction: 4.

Public submissions on the interim decision

One submission was received. The submission supported the proposal but suggested adding the words "excluding derivatives" to the proposed schedule entries to ensure no other substances are inadvertently captured.

Delegate's final decision

The delegate notes the submission that essentially supports the interim decision, although requesting the addition of words "excluding derivatives" to the proposed entries. No evidence was presented to show that any derivatives would be inadvertently captured by the proposed entries, or that the toxicological profiles of any such derivatives would be sufficiently different from the listed chemical. Accordingly, the delegate has confirmed the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The implementation date is 1 October 2016.

1.3 Chrysoidine base

Referred Delegate's scheduling proposal

- In response to issues raised in a NICNAS IMAP Human Health Tier 2 assessment report on chrysoidine base and its salts, the scheduling proposal is to create a new Schedule 6 entry for chrysoidine base to regulate its use in domestic and cosmetic products.

Applicant's application and scheduling proposal

In December 2015, NICNAS under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme referred the following proposal to be considered by the delegate:

> Appropriate scheduling and labelling should be undertaken to mitigate risk when chrysoidine base and its salts are used in domestic and cosmetic products. Due to their toxicity profile, these chemicals should be considered for listing in Schedule 6 of the SUSMP.

The reasons for the request were as follows:

- Currently, there are no restrictions on introducing or using these chemicals in Australia. In the absence of any regulatory controls, the characterised critical health effects (particularly carcinogenicity and mutagenicity) have the potential to pose an unreasonable risk if the chemical is used in cosmetic products. Whilst domestic use of the chemicals will result in lower levels of

exposure, given that the chemicals are genotoxic there is sufficient uncertainty regarding the safety of such products to warrant some restriction.

- Although use in cosmetic and/or domestic products in Australia is not known, the chemicals are reported to be used in cosmetic and/or domestic products overseas, such as shoe polish and hair dyes that could result in exposure of the general population.
- The chemicals are classified as genotoxic.
- Whilst data for carcinogenicity of the chemicals themselves is limited, chrysoidine hydrochloride (Basic Orange 2) has produced liver tumours in mice. Solvent Orange 3 is predicted to be carcinogenic based on QSAR modelling.
- Three structurally-related azo aromatic amines are considered to be carcinogenic, all producing liver tumours in rats and/or mice as well as tumours in other organs. Where comparisons could be made using the available data, the chemicals being assessed had similar genotoxicity profiles to these structurally-related azo aromatic amines.
- Azo dyes derived from two of the three structurally related aromatic amines (*p*-aminoazobenzene and *o*-aminoazotoluene) have recently had a decision published for their inclusion in Schedule 7.

The chemicals are prohibited for use in hair dye products in a number of overseas countries.

Substance summary

The NICNAS IMAP Tier II Human Health Report on Chrysoidine base and its salts, the *p*-aminobenzene IMAP report and the *o*-aminoazotoluene IMAP Report are available from the NICNAS website.

The chemicals in this group include chrysoidine base (Solvent Orange 3—CAS No. 495-54-5) and various salts of chrysoidine.

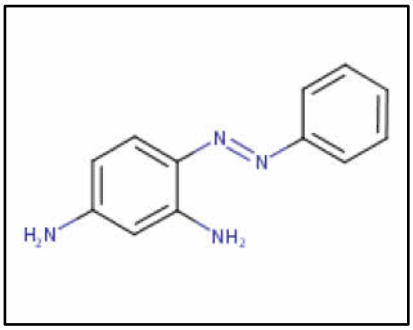

Figure 3. Structure of chrysoidine base

The critical concern for this group of chemicals relates to the potential for carcinogenic effects following exposure, due to the presence of the chrysoidine base. The chemicals are all classified as genotoxic.

Data are available for Basic orange 2 which is the hydrochloride salt of chysoidine base and structurally-related azo aromatic amines, p-aminoazobenzene (CAS No. 60-09-3), o-aminoazotoluene (CAS No. 97-56-3) and phenazopyridine hydrochloride (CAS No. 136-40-3).

Acute toxicity

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

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50}	Rat	1532 mg/kg bw	Schedule 6
Skin irritation		Irritant (limited data)	Schedule 5
Eye irritation		Severe (limited data)	Schedule 6
Skin sensitisation		Analogue data – skin sensitiser	Schedule 5

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

The chemicals are classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the Hazardous Substance Information System (HSIS) (Safe Work Australia). Based on test results, the chemicals have low to moderate acute oral toxicity in rats. Chrysoidine base has a median lethal dose (LD_{50}) in the range warranting classification and there is insufficient evidence to determine the LD_{50} for the remaining chemicals.

Irritation

The chemicals are classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). No data are available to evaluate this classification.

All the chemicals in this group (except Solvent Orange 3: CAS No. 495-54-5) are currently classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). No data are available to evaluate this classification. However, in the absence of information, and as the classification is not clearly related to extremes of pH, this hazard classification is also considered appropriate for Solvent Orange 3.

Sensitisation

No data on skin sensitisation are available for the chemicals. The structurally-related chemicals, p-aminoazobenzene (CAS No. 60-09-3) and o-aminoazotoluene (CAS No. 97-56-3), are considered to be sensitisers based on observations in animals and humans. In addition, the chemicals in this group have the potential to form benzenamine (CAS No. 62-53-3) due to potential azo reduction by the skin microflora. Benzenamine is classified as a sensitiser in the HSIS with available animal data to support this classification. Overall a classification is considered to be warranted.

Repeat-dose toxicity

The data for repeated dose toxicity for this chemical group are limited. However, repeated dose exposure of rats to 160 mg/kg bw/day of Basic Orange 2 for 21 days resulted in pathological changes to blood and stomach tissue. Whilst effects are not sufficient for classification, effects in the blood are consistent with those observed with the structurally related chemical, p-aminoazobenzene (CAS No. 60-09-3), and its potential metabolite, benzenamine and, therefore, the blood is considered to be a likely target for systemic toxicity for this group of chemicals.

Genotoxicity

The chemicals are classified as hazardous (Category 3 mutagenic substances) with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in HSIS (Safe Work Australia). The positive *in vitro* and *in vivo* genotoxicity data on some of the chemicals of this group (Solvent Orange 3, Basic Orange 2 and chrysoidine monoacetate—CAS No. 75660-25-2) and the metabolite chemicals support this classification.

Carcinogenicity

Limited data are available for the chemicals. Based on the weight of evidence from available data on one of the chemicals in the group (Basic Orange 2), similar azo aromatic amines, p-aminoazobenzene, o-aminoazotoluene and phenazopyridine hydrochloride, and the metabolite chemical (benzenamine), the chemicals are considered carcinogenic. This is supported by the available genotoxicity data for the chemicals and information available from Quantitative Structure Activity Relationship modelling.

Data for the chemicals

Basic Orange 2 was tested for carcinogenicity in single experiments in mice and rats using oral administration (IARC, 1987). Significantly increased incidences of liver adenomas and adenocarcinomas (72 %) and leukaemia and reticular cell sarcomas (with a combined incidence of 27 %) compared with controls were observed in C57BL mice that were fed a low-vitamin diet containing 0.2 % chrysoidine (equivalent to 260 mg/kg bw/day) for 13 months. Metastases of the liver tumours to the lungs were also observed. The second experiment on rats was inadequately reported. No tumours occurred in a group of 10 rats fed a diet containing 0.1 % chrysoidine (equivalent to 50 mg/kg bw/day) for 51–366 days. However, the experiment was performed with only a low dose administered to a small number of animals with short exposure and observation periods, and, therefore, may not have fully explored the carcinogenic potential of the chemical in rats.

Analogue data

The structurally-related azo aromatic amines, p-aminoazobenzene (CAS No. 60-09-3), o-aminoazotoluene (CAS No. 97-56-3) and phenazopyridine hydrochloride (CAS No. 136-40-3), are all reported to cause liver tumours in rats and/or mice. Other sites of tumour formation include the lung (p-aminoazobenzene and o-aminoazotoluene), the colon (phenazopyridine hydrochloride) and urinary bladder, gall bladder, and mammary gland (o-aminoazotoluene). The chemicals, p-aminoazobenzene and o-aminoazotoluene, are classified as hazardous (Category 2 carcinogenic substances) with the risk phrase 'May cause cancer' (T; R45) in the HSIS (Attachments B and C The metabolite benzenamine (CAS No. 62-53-3) is carcinogenic to rats (albeit at higher doses and with effects observed in the spleen) and is classified as a Category 3 carcinogenic substance in the HSIS.

QSAR/mechanistic data

QSAR modelling for the Solvent Orange 3 using OASIS-TIMES, gave positive predictions for carcinogenicity. However, the chemical structure was out of the applicable domain of the QSAR models indicating greater uncertainty about the reliability of the positive predictions.

The chemicals may undergo metabolism to produce reactive nitrenium ions as an initial step in the carcinogenic mechanism of action. This usually involves N-hydroxylation of the aromatic amines to an N-hydroxylamine and eventual formation of the pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions may covalently bind to DNA provided that they are sufficiently stabilised to not undergo further reactions. It was shown in an Ames test (with metabolic activation) that the stability of the nitrenium ions is correlated with mutagenicity (Benigni and Bossa, 2011). The non-fused conjugated ring polycyclic aromatic amine component of the chemical is postulated to stabilise the formation of the reactive nitrenium ions. The other chemicals in this group, being salts of Solvent Orange 3, are expected to behave similarly.

Reproduction and developmental toxicity

No data are available for the chemicals.

Observation in humans

Human evidence of carcinogenicity, based on exposure to chrysoidine, is considered to be limited (IARC, 1987). Reports of bladder cancer from oral exposure in three amateur fishermen in the United Kingdom exposed to chrysoidine-dyed maggots led to an additional four cases being reported and two case–control studies. A bladder cancer case-control study involving approximately 900 case-control

pairs found a relative risk of 0.7 based on five cases for bronze maggots and 2.0 based on nine cases for yellow maggots (Cartwright et al., 1983). A smaller study (202 case-control pairs) showed more bladder cancers following the use of dyed maggots (14 % cases, 8 % controls), with a 3-fold risk when bronze maggots were used for more than five years (Sole and Sorahan, 1985).

Public exposure

Although the uses of these chemicals in cosmetic and/or domestic products in Australia are not known, the chemicals are reported to be used in products overseas such as shoe polish and hair dyes, which might result in exposure of the general population. The introduction of these dyes for home use cannot be excluded.

International regulations

The chemicals are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II (Ref # 1293): List of substances which cosmetic products must not contain (CosIng).
- New Zealand Cosmetic Products Group Standard—Schedule 4 (Ref # 1293): Components cosmetic products must not contain; and
- 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.

In the above directives, the chemicals are listed as 'm-phenylenediamine, 4-(phenylazo)-, and its salts, when used as a substance in hair dye products'.

In 2004, the Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP) concluded that Basic Orange 2 cannot be considered safe for hair dyeing purposes, unless these purposes are regarded as safe on the basis of an adequate safety dossier (SCCNFP, 2004).

Current scheduling status

Chrysoidine base is not specifically scheduled.

Scheduling history

Chrysoidine base 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 aligning the scheduling controls for this substance with the EU and noted all of the substances identified in the NICNAS IMAP report are listed in Annex II of the EU Cosmetics Regulations and cannot be used in cosmetics in the EU. They believe the schedule entry should specifically identify the following CAS numbers to ensure no other substances are inadvertently captured. CAS No. 495-54-5; 532-82-1; 63681-54-9; 75660-25-2; 79234-33-6; and 94247-67-3, consistent with the entry for Benzidine based azo-dyes.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

The committee provided the following advice in response to the Delegate's questions:

- The committee agreed there was insufficient evidence of genotoxicity and carcinogenicity to warrant a Schedule 7 entry. Acute toxicity data were consistent with Schedule 6 rather than Schedule 7. The committee agreed it was better to have a specific entry for this chemical rather

than capturing it in the other scheduled dyes entries. Further it was noted that there is evidence of use in the hobby industry, and this should be considered when scheduling the substance.

- The committee noted that inclusion of the substance in Schedule 6 will effectively preclude use of chrysoidine and its salts in cosmetics (due to the requirement for POISON labelling), but this would not prevent use of these substances in hair dye products, noting that there are many hair dye products that contain other substances in the consumer market with the POISON signal heading.
- The committee agreed that given the information before them, Schedule 6 and Schedule 10 entries are warranted to prohibit use in hair dyes with Appendix E statements in relation to skin and eyes.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) toxicity - Acute toxicity data are consistent with Schedule 6 criteria; f) other – There was concern with potential for eye irritation. Recommended schedule amendments would apply regulatory controls consistent with those in place internationally.

The committee advised that a combination of a Schedule 6 entry with a Schedule 10 entry be created for chrysoidine with appropriate specifications as follows:

Schedule 6 - New Entry

CHRYSOIDINE **except** when in Schedule 10.

Schedule 10 - New Entry

CHRYSOIDINE in preparations for use in hair dyes.

Appendix E, Part 3 - New Entry

CHRYSOIDINE.

Standard statements: A, E1.

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 notes and accepts, the advice of the ACCS to create new listings for Chrysoidine in Schedules 6 and 10, and in Appendix E. The delegate notes the industry submission that requests the inclusion of CAS numbers for the six substances that would be captured by these entries, but also notes ACCS advice that listing under the name chrysoidine would automatically capture all the salts and derivatives listed in the NICNAS IMAP report, under the provisions of clause 2(c) of Part 1 of the Poisons Standard. The delegate also notes that this substance would not be captured under any existing Schedule entries for phenylenediamines or azo dyes.

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

The purpose of the Schedule 10 entry is to restrict use in hair dyes preparations, in alignment with similar restrictions in international cosmetics regulations (EU, NZ and ASEAN). The toxicological basis for this restriction is the acute toxicity profile, including skin sensitisation potential and limited evidence of genotoxicity and carcinogenicity. For use in products other than hair dyes, the listings in Schedule 6 and Appendix E should provide suitable warnings to product users, including the requirement for the signal heading POISON on product labels. There was insufficient information, and no recommendation from the ACCS, for the delegate to consider any low concentration exemptions from the proposed entries.

The proposed implementation date is **1 October 2016**. An early implementation date is proposed in order to bring the regulation of this hair dye ingredient in products sold in Australia into alignment with international regulations.

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

Schedule 6 - New Entry

CHRYSOIDINE **except** when in Schedule 10

Schedule 10 - New Entry

CHRYSOIDINE in preparations for use in hair dyes.

Appendix E, Part 3 - New Entry

CHRYSOIDINE.

Standard statements: A, S1 (wash off skin), E1 (wash out of eyes)

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

1.4 p-Aminophenol

Referred Delegate's scheduling proposal

· In response to issues raised in a NICNAS IMAP Human Health Tier 2 assessment report, the scheduling proposal is to create a new Schedule 6 entry for *p*-aminophenol with appropriate exemption and cut-off to regulate its use in hair dyes and eyelash colouring products.

Applicant's application and scheduling proposal

In December 2015, NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the following proposal to be considered by the delegate:

· A proposal to create a new entry for p-aminophenol in Schedule 6 of the SUSMP for use in hair dyes.

The reasons for the request are:

· *p*-aminophenol has reported cosmetic use in permanent hair dye preparations in Australia;

- *p*-aminophenol is a skin sensitiser and is mutagenic;
- overseas information indicates that the chemical is to be used in oxidative hair dye formulations and in the bottle on the market at a maximum concentration of 1.8% and be typically mixed in a 1:1 ratio with an oxidative agent thereby reaching a concentration of 0.9% for in use application (SCCP, 2005);
- the overseas restrictions for use of this chemical in hair dyes (EU Cosmetic Regulation Annex III) indicate that the maximum concentration applied to hair must not exceed 0.9 % (after mixing under oxidative conditions).

The critical health effects for risk characterisation are mutagenicity and skin sensitisation. Given the potential for mutagenicity and skin sensitisation, the risk would be better controlled by inclusion of warning statements on the label for preparations containing the chemical at any concentration. This chemical has similar use and hazard profile to a number of chemicals which have been listed in Schedule 6 with reverse scheduling requirements.

Substance summary

Please refer to the NICNAS IMAP Tier II report for p-aminophenol that is publicly available on the NICNAS website.

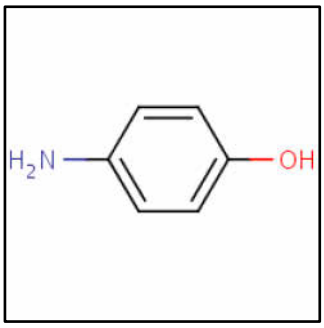

Figure 4. Structure of *p*-aminophenol

Acute toxicity

The acute toxicity end-points for *p*-aminophenol are listed in the table below.

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	671 (SD rats)	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5000	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>3.42 mg/L	N/A
Skin irritation	Rabbit	Slight irritant	Schedule 5
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (maximisation test and Buehler test)	Guinea pig	Skin sensitiser	Schedule 6
Skin sensitisation (human data)	Human		

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

The chemical has moderate acute oral toxicity and low acute dermal toxicity. The available data for inhalation were inconclusive.

Irritation

Based on the available information, *p*-aminophenol is a slight skin and eye irritant.

Sensitisation

Based on the available animal and human data, *p*-aminophenol is a skin sensitiser.

In a study similar to the Buehler test, Pirbright Dunkin Hartley guinea pigs were treated with 0.1, 0.5, 1 or 2 % preparations of p-aminophenol. Dose-dependent, positive skin responses were observed in 3/10, 5/10, 6/10 and 9/10 animals, respectively.

Freund's complete adjuvant tests were conducted in guinea pigs using two methods of induction. In the first method, Freund's adjuvant was injected alone before 0.18 mmol/L of p-aminophenol was topically administered twice (over two days); p-aminophenol did not induce any skin sensitisation reactions. In the second method, Freund's adjuvant was injected with 0.18 mmol/L of p-aminophenol (ratio 1:1) (induction), followed by a 0.09 mmol/L of p-aminophenol 16 days later (challenge). The treatment induced positive reactions in 40 % of the animals.

P-aminophenol gave positive skin reactions in patch tests in 25 % (1/4) and 17 % (2/12) of patients with dermatitis (among 13 beauticians and 33 hairdressers respectively, tested for occupational dermatitis).

Among 24 hairdressers and eight barbers patch tested for occupational allergic contact dermatitis, p-aminophenol induced positive reactions in 25 % (2/8) of patients with dermatitis.

The application of p-aminophenol at 1 % gave positive results in 3 % (11/372) of patients patch tested with the chemical.

Repeat-dose toxicity

Based on the available data, p-aminophenol may cause severe effects from repeated oral exposure. The kidney is the target organ for repeated oral toxicity in rats, with nephrosis seen at doses of 30 mg/kg bw/day and above. However, there are uncertainties about the reversibility of kidney effects.

Genotoxicity

Based on the available *in vitro* and *in vivo* data, p-aminophenol may have mutagenic properties. Most of the *in vivo* tests conducted gave positive results for genotoxicity on somatic cells, including:

- a significant increase in micronucleated polychromatic erythrocytes and inhibition of bone marrow cell proliferation in male CD1 mice orally administered the chemical at 125, 250 or 500 mg/kg bw in a micronucleus test (OECD TG 474);
- positive results in four other micronucleus tests in mice receiving doses of the chemical up to 214.5 mg/kg bw (oral) or 872 mg/kg bw (intraperitoneal);
- positive results for somatic mutations and recombinations (SMAR) in *D. melanogaster* fed with 20 mmol/L of p-aminophenol;
- negative results in sex-linked recessive lethal (SLRL) test in *D. melanogaster* administered the chemical at doses up to 130 mmol/L (oral) or 30 mmol/L (injection); and
- negative results in a dominant lethal test in male SD rats fed with *p*-aminophenol at doses up to 467 mg/kg bw/day for 20 weeks.

Carcinogenicity

Based on the limited information available, *p*-aminophenol is not expected to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, *p*-aminophenol is not expected to have reproductive or developmental toxicity. The foetal effects observed in rats at high doses (133 and 467 mg/kg bw/day) are considered secondary to maternal toxicity.

Public exposure

The chemical was reported to be used in permanent hair dyes in Australia in 2007.

Currently, there are no restrictions in Australia on using p-aminophenol in hair dyes. In the absence of any regulatory controls, the characterised critical health effects, particularly skin sensitisation and mutagenicity, have the potential to pose an unreasonable risk under the identified use. The risk could be mitigated by implementing restrictions for the use of the chemical in hair dyes.

International regulations

Using p-aminophenol in hair dyes in the EU is subject to the restrictions described in EU Regulation Annex III (amended by Regulation (EC) No 1197/2013): after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 0.9 %.

Current scheduling status

p-Aminophenol is not specifically scheduled.

Scheduling history

p-Aminophenol 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 aligning the scheduling controls with EU. They note substance is included in Annex III of the EU Cosmetics Regulations, restricting its use to oxidative hair dyes with in-use concentration not exceeding 0.9%. They propose schedule entry consistent with recent decisions on oxidative hair dye ingredients. They also request a later implementation date to allow time for relabelling of products already on the market.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

The committee advised that the toxicological profile of p-aminophenol warrants controls over use in cosmetics and consumer products, as well as other products. Members agreed that a Schedule 6 entry is appropriate according to SPF criteria. On the evidence supporting a cut off concentration, the committee agreed there was sufficient data to recommend a 1% cut off concentration. The committee did not consider the evidence for mutagenicity was sufficient to recommend a higher schedule.

The committee advised that the appropriate name for use in the SUSMP was p-aminophenol and a new Schedule 6 entry be created for p-aminophenol with appropriate exemptions and cut off as follows:

Schedule 6 - New Entry

p-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of p-aminophenol 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 E, Part 2 - New Entry

p-AMINOPHENOL.

Standard statements: A, S1.

Appendix F, Part 3 - New Entry

p-AMINOPHENOL.

Warning Statement: 28.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: a) risk of skin sensitisation is reduced by limiting maximum concentration in bottle and after mixing. c) toxicity - the acute oral toxicity and skin sensitisation are consistent with Schedule 6 criteria. d) The positive skin sensitisation is dose-dependent and therefore Schedule 6 with appropriate RASML is appropriate.

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

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.

p-Aminophenol is one of four oxidant hair dyes that were referred to the March 2016 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

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

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-aminophenol should be listed in Schedule 6, with an exemption cut-off at 1%, provided products are labelled with the warning statements about skin sensitisation potential that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that the potential for eye irritation is not sufficient to require warning statements relating to use for dyeing eyebrows and eyelashes.

The proposed implementation date is **1 June 2017** to allow for an orderly process of re-labelling of products already on the market.

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

Schedule 6 - New Entry

p-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of p-aminophenol 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 E, Part 2 - New Entry

p-AMINOPHENOL.

Standard statements: A, S1.

Appendix F, Part 3 - New Entry

p-AMINOPHENOL.

Warning Statement: 28.

Public submissions on the interim decision

One submission was received. The submission suggested adding the words “excluding derivatives” to the proposed schedule entry to ensure no other substances are not inadvertently captured.

Delegate’s final decision

The delegate notes the submission that essentially supports the interim decision, although requesting the addition of words “excluding derivatives” to the proposed entries. No evidence was presented to show that any derivatives would be inadvertently captured by the proposed entries, or that the toxicological profiles of any such derivatives would be sufficiently different from the listed chemical. Accordingly, the delegate has confirmed the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The implementation date is 1 June 2017.

1.5 2-Methylresorcinol

Referred Delegate's scheduling proposal

- In response to issues raised in a NICNAS IMAP Human Health Tier 2 assessment report on 2-methylresorcinol, the scheduling proposal is to create a new Schedule 6 entry for 2-methylresorcinol, with appropriate exemption and cut-off to regulate its use in hair dye and eyelash colouring products.

Applicant's application and scheduling proposal

In December 2015, the NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the following proposal to be considered by the delegate:

- To create a new entry for 1,3-benzenediol, 2-methyl- in Schedule 6 of the SUSMP with an appropriate cut-off to use in hair dyes.

The reasons for the request are:

- the chemical is a severe eye irritant and weak skin sensitiser;
- the chemical has moderate acute oral toxicity; and
- International restrictions for use of this chemical in hair dyes (the maximum concentration allowed on hair is 1.8 %) (SCCS, 2008).

Substance summary

Please refer to the NICNAS IMAP assessment report for 1,3-benzenediol, 2-methyl-. This report is publicly available on the NICNAS website.

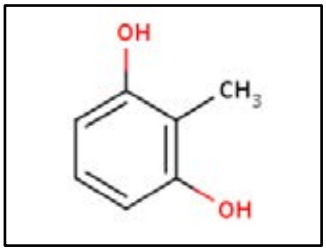

Figure 5. Structure of 1,3-benzenediol, 2-methyl- (2-methylresorcinol)

Acute toxicity

The acute toxicity end-points for **2-methylresorcinol** are listed in the table below.

Toxicity	Species	Results	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Mice	390	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	Mild irritant	Schedule 5
Eye irritation	Rabbit	Severe irritant	Schedule 6
Skin sensitisation (local lymph node assay (LLNA))	Mice	Weak sensitiser (EC3 = 50 %)	Schedule 5/6

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

Based on available data, the chemical has moderate acute oral toxicity. No data are available on acute dermal and inhalation toxicity.

Skin irritation

2-Methylresorcinol is considered to be slightly irritating to skin. In an OECD Guideline 404 compliant study, 0.5 g of the test material was moistened and applied to the intact, shaved back skin of rabbits (three males/group) for four hours under semi-occlusive patches. Very slight erythema developed in one animal after one hour.

Eye irritation

2-Methylresorcinol is a severe eye irritant. In a OECD guideline 405 study, 0.1 mL of undiluted test chemical (equivalent to 50.6 mg) was instilled into one eye of one rabbit and left for 24 hours. The test chemical caused corneal opacity (maximum grade 3) and epithelial damage (maximum 100 % of the corneal surface). These effects were not fully reversible within the observation period. Iridial irritation (grade 1) was observed for the first seven days of observation. Conjunctival irritation (consisting of erythema and chemosis) was observed. The nictitating membrane and eyelids exhibited white discolouration, consistent with necrosis.

Sensitisation

2-Methylresorcinol is a weak skin sensitiser, according to a LLNA assay conducted CBA mice (5/group) had 25 µL of the test material (at 1, 10, 25 or 50 %) applied to the dorsal surface of each ear, once daily for three consecutive days. Five days after the first topical application, all mice were administered radiolabelled thymidine (3HTdR), draining lymph nodes were excised and thymidine incorporation into the lymph node cells was assessed. Stimulation Indices (SI) of 0.7, 0.6, 1.1 and 3 were calculated for the 1, 10, 25 and 50 % groups, respectively. An EC 3 of 50 % was determined accordingly.

Repeat-dose toxicity

Based on the data available, 2-methylresorcinol 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 weight of evidence from the available well-conducted *in vitro* and *in vivo* genotoxicity studies, 2-methylresorcinol is not considered to be genotoxic.

Carcinogenicity

No data were available.

Reproduction and developmental toxicity

Based on the available data, 2-methylresorcinol is not expected to have reproductive or developmental toxicity.

Public exposure

2-Methylresorcinol is reported to be used in permanent hair dye preparations in Australia.

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

The following international regulations apply:

- EU Cosmetic Directive 76/768/EEC Annex III Part 1: List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down-maximum concentration in ready to use formulation; 1.8 %;
- ASEAN Cosmetic Directive Annex III-Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;

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.

Current scheduling status

2-Methylresorcinol is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One public submission was received. The submission had no objections to aligning the scheduling controls for this substance with the EU. The submission noted that 2-methylresorcinol is included in Annex III of the EU Cosmetics Regulations, restricting its use to hair dyes with in-use concentration not exceeding 1.8%. They proposed a specific Schedule entry in line with recent decisions on hair dye products. They also sought a later implementation date to allow relabelling of existing products.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's questions, the Committee advised that the toxicological profile of the substance warrants controls over use in hair dye products, including warning statements indicating products should not be used for dying eyebrows/eye lashes. The committee advised the toxicity profile of the substance was consistent with inclusion in Schedule 6.

In regards to the sensitization potential of the substance, the committee advised that, with a suitable cut off concentration consistent with that in the EU, the risk of sensitization from use of the hair dye products was low. As such, the Committee recommended a cut off concentration of 1.8%.

Members agreed 2-methylresorcinol was an appropriate name and consistent with the INCI name.

The committee recommended that a new Schedule 6 entry be created for 2-methylresorcinol with appropriate exemptions and cut off as follows:

Schedule 6—New Entry

2-METHYLRESORCINOL **except**:

a) in non-oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – 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 1.8 per cent or less of 2-methylresorcinol 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 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, Part 2 - New Entry

2-METHYLRESORCINOL

Standard statements: A, E1

Appendix F, Part 3 - New Entry

2-METHYLRESORCINOL

Safety direction: 1

The committee recommended a late implementation date (1 February 2017) to allow relabelling of existing products on the market.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: a) Potential for severe eye damage when used as a hair dye, particularly eyebrow and eyelash tinting products; c) It is a severe eye irritant and has an acute LD_{50} of 390mg/kg bw which warrants a Schedule 6 entry. Exposure would occur to the public and professional users of hair colourants; d) Restricted to 1.8% for hair dye only.

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

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

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

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.

2-methylresorcinol is one of four oxidant hair dyes that were referred to the March 2016 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-methylresorcinol should be listed in Schedule 6, with an exemption cut-off at 1.8% in products either without, or after, mixing with an oxidant, provided products are labelled with the warning statements about skin sensitisation potential that have been required for similar oxidative hair dyes. The delegate also notes ACCS advice that the potential for eye irritation is sufficient to require additional warning statements relating to use for dyeing eyebrows and eyelashes.

The delegate also notes ACCS advice that 2-methylresorcinol is the INCI name and is the preferred name for listing in Schedule 6.

The proposed implementation date is **1 June 2017** to allow for an orderly process of re-labelling of products already on the market.

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

Schedule 6 - New Entry

2-METHYLRESORCINOL **except**:

a) in non-oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol when the immediate container and primary pack are labelled with the following statements:

    KEEP OUT OF REACH OF CHILDREN, and

    WARNING – 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 1.8 per cent or less of 2-methylresorcinol 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 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, Part 2 - New Entry

2-METHYLRESORCINOL.

Standard statements: A, E1.

Appendix F, Part 3 - New Entry

2-METHYLRESORCINOL.

Safety direction: 1.

Public submissions on the interim decision

One submission was received. The submission supported the proposal but suggested adding the words "excluding salts and derivatives" to the proposed schedule entry to ensure no other substances are inadvertently captured. The submission further noted that some derivatives of resorcinol are restricted or banned in the EU for certain uses, but controls on each differ. Consequently, the submission recommended the proposed schedule entry be amended to exclude salts and derivatives, and other derivatives should be considered separately for scheduling to ensure appropriate scheduling controls are applied in each separate case.

Delegate's final decision

The delegate notes the submission that essentially supports the interim decision, although requesting the addition of words "excluding salts and derivatives" to the proposed entries. No evidence was presented to show that any salts or derivatives would be inadvertently captured by the proposed entries, or that the toxicological profiles of any such salts or derivatives would be sufficiently different from the listed chemical. The delegate notes that it has not been deemed necessary to add the words "excluding salts and derivatives" to other oxidative hair dye ingredient entries in Schedules 5 or 6.

The delegate further notes that some of the resorcinol 'derivatives' specified in the submission (e.g. 4-chlororesorcinol, 4-(phenylazo)resorcinol, hexylresorcinol, 4-isobutylresorcinol and phenylethyl resorcinol) would not be considered as 'derivatives' as defined in Part 1 of the Poisons Standard, but that consideration may need to be given to scheduling of these substances individually. Accordingly the delegate will draw the attention of NICNAS to the potential uses of these substances in Australian products.

The delegate has confirmed the interim decision relating to 2-methylresorcinol. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The implementation date is 1 June 2017.

1.6 2,4-Diamino-5-methylphenetole

Referred Delegate's scheduling proposal

- In response to issues raised in a NICNAS IMAP Human Health Tier 2 assessment report on 2,4-diamino-5-methylphenetole, the scheduling proposal is to create a new Schedule 6 entry for 2,4-diamino-5-methylphenetole with an appropriate exemption and cut off to regulate its use in hair dyes and eyelash colouring products.

Applicant's application and scheduling proposal

In December 2015, the NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, referred the following proposal to be considered by the delegate:

- A proposal to create a new entry for 2,4-diamino-5-methylphenetole hydrochloride in Schedule 6 of the SUSMP to include use in hair dyes and eyelash colouring products.

The reasons for the request are:

- 2,4-diamino-5-methylphenetole has reported cosmetic use overseas in permanent hair dye preparations;
- 2,4-diamino-5-methylphenetole could have moderate skin sensitisation potential;

- lack of data on reproductive and developmental toxicity, and acute or repeated dose dermal and inhalation toxicity; and
- the use of 2,4-diamino-5-methylphenetole in cosmetics is prohibited overseas. 2,4-diamino-5-methylphenetole is prohibited by the Commission Directive 2006/65/EC as 'permanent hair dye substances for which no explicit interest was expressed during the public consultation in defence of their use in hair dyes' (EC, 2006).

The critical health effect for risk characterisation is skin sensitisation. Given the potential for skin sensitisation, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical at any concentration. Similar chemicals have been listed in Schedule 6 of the SUSMP with reverse scheduling requirements.

Substance summary

Please refer to the publicly available report on the NICNAS website.

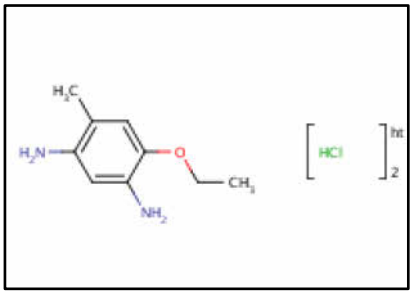

Figure 6. Structure of 2,4-diamino-5-methylphenetole.

Acute toxicity

The acute toxicity end-points for 2,4-diamino-5-methylphenetole are listed in the table below.

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat and mouse	Approximately 200-2000	Schedule 6
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	Guinea pig	Not an irritant at 3 % concentration	N/A
Eye irritation	Guinea pig	Not an irritant at 3 % concentration	N/A
Skin sensitisation: QSAR - LLNA	N/A	Skin sensitiser (predicted EC3 = 5.1)	Schedule 6

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

Based on the available data, 2,4-diamino-5-methylphenetole has been reported to have moderate acute oral toxicity, although the data are not sufficient to validate this conclusion. No information was available for acute toxicity by dermal and inhalation routes.

Irritation

Based on the available data, 2,4-diamino-5-methylphenetole is not irritating to the skin and eyes at a 3 % concentration.

Sensitisation

Based on the available data, 2,4-diamino-5-methylphenetole is expected to be a skin sensitiser.

Ten female guinea pigs were induced with a 0.1 % solution of 2,4-diamino-5-methylphenetole in Ringer's solution via intradermal injection to the clipped shoulder region, followed by a topical application of a 40 % solution of 2,4-diamino-5-methylphenetole. After two weeks, the animals were challenged with a 30 % solution of the chemical. Two of 10 test animals showed slight to moderate erythema (EC SCC, 2000). The SCCNFP (1999) reported that this study used an intradermal induction concentration that was too low. The cosmetic product containing the chemical was reported to have a label warning for risk of sensitisation (SCCNFP, 1999).

The sensitisation potency of 2,4-diamino-5-methylphenetole was predicted in a study on 229 hair dye substances using a QSAR model based on the LLNA. The study predicted the chemical to be a moderate to strong sensitiser, with an estimated concentration needed to produce a 3-fold increase in lymphocyte proliferation (EC3) value of 5.1 (Sosted *et al*., 2004).

Repeat-dose toxicity

Based on the available data, 2,4-diamino-5-methylphenetole 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, 2,4-diamino-5-methylphenetole is not considered to be genotoxic.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of 2,4-diamino-5-methylphenetole. Based on the available genotoxic data and information available from QSAR modelling, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Limited data are available and are not sufficient to derive a conclusion on the reproductive and developmental toxicity of 2,4-diamino-5-methylphenetole.

Observation in humans

No information was available.

Public exposure

2,4-diamino-5-methylphenetole was not reported to be used in hair dye preparations in Australia in 2007. It has overseas use in hair dye preparations at a maximum concentration of 2 % (maximum concentration of 1 % when mixed with hydrogen peroxide) (SCCNFP, 1999).

The Association of South East Asian Nations (ASEAN), European Union (EU) and New Zealand Cosmetic Products Group Standard have prohibited the use of this chemical in cosmetics. 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 if used in cosmetics.

International regulations

The chemical is listed on the following:

- EU Cosmetic Directive 76/768/EEC Annex II—List of Substances which must not form part of the composition of cosmetic products;
- EU Commission Directive 2006/65/EC of 19 July 2006 amending Council Directive 76/768/EEC;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- ASEAN Cosmetic Directive Annex II—Part 1: List of substances which must not form part of the composition of cosmetic products.

Current scheduling status

2,4-diamino-5-methylphenetole is not specifically scheduled.

Scheduling history

2,4-diamino-5-methylphenetole 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 no objections to aligning the scheduling controls for this substance with the EU were raised. The submission notes that 2,4-diamino-5-methylphenetole is listed in Annex II of the EU Cosmetics Regulations and cannot be used in cosmetics in the EU.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's questions, the Committee advised the toxicity profile of the substance warrants control over use in cosmetics and consumer products. The committee agreed a Schedule 6 entry for phenylenediamines was appropriate and with no exemption cut off concentration specified. The committee advised that inclusion in Schedule 6 effectively prohibits use of 2,4-diamino-5-methylphenetole in cosmetics.

The committee advised that 2,4-diamino-5-methylphenetole does not require separate scheduling, as the substance is considered to already be captured by the existing entries for phenylenediamines. However the Committee advised that the substance should be included in the index with cross reference to the general entry to provide clarity for industry on its scheduling. This editorial change will be included in the next update of the SUSMP.

The Committee recommended an early implementation date for the index amendment.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: a) low risk with oral toxicity as it is for topical use; b) Chemical has reported use overseas in cosmetic preparations. No reports of use in Australia; c) substance demonstrates skin sensitisation and acute oral toxicity consistent with Schedule 6 criteria; d) appropriate to use labelling similar to that used by other Schedule 6 oxidative hair colourant chemicals; f) the committee considered the substance was already captured by the existing entry for phenylenediamines and does not warrant separate scheduling.

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

2,4-Diamino-5-methylphenetole is one of four oxidant hair dyes that were referred to the March 2016 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 the toxicity profile of 2,4-diamino-5-methylphenetole is consistent with other phenylenediamine-based hair dye ingredients and that it could be considered to be covered by the generic Schedule 6 listing for PHENYLENEDIAMINES. Accordingly, the only scheduling action proposed is to cross-reference 2,4-diamino-5-methylphenetole in the index with the generic entry.

An implementation date is not relevant, since the substance is already covered by the generic PHENYLENEDIAMINES entry. The addition of the index cross-reference should be done at the earliest possible time.

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

Index - New Entry

2,4-DIAMINO-5-METHYLPHENETOLE
cross reference: PHENYLENEDIAMINES

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

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

1.7 2-Chloro-5-Nitro-N-Hydroxyethyl-p-Phenylenediamine

Referred Delegate's scheduling proposal

- In response to issues raised in a NICNAS IMAP Human Health Tier 2 assessment report on 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine, the scheduling proposal is to create a new Schedule 6 entry for 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine with an appropriate exemption and cut-off to regulate its use in hair dye and eyelash colouring products.

Applicant's application and scheduling proposal

In December 2015, NICNAS, under its IMAP programme referred the following proposal to be considered by the delegate:

- A proposal to create a new entry for the chemical in Schedule 6 of the SUSMP to include use in hair dyes, other hair products and eyelash colouring products.

The reasons for the request are:

- the chemical has reported cosmetic use in permanent and semi-permanent hair dye preparations in Australia;
- overseas use indicate that 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine a maximum concentration of 2 % is to be included in hair dyes and 1 % concentration in hair tinting and colour setting lotions (EC SCC, 2000);
- the chemical is potentially a moderate to strong skin sensitiser;
- only limited data are available for eye and skin irritation, indicating low concentrations of the chemical could be slightly irritating to the eyes and non-irritating to the skin;
- there is a lack of data on acute dermal and inhalation toxicity, repeated dose inhalation toxicity, and reproductive and developmental toxicity;
- many countries, including those in the European Union, have banned the use of 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine in cosmetics. The chemical is regulated by the EU Commission Directive 2007/54/EC for 'Substances for which no updated safety files are submitted allowing an adequate risk assessment should be included in Annex II' (EC, 2007).

The critical health effect is the potential for skin sensitisation, and this risk would be better controlled by inclusion of warning statements on the label of preparations containing 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine at any concentration. Similar chemicals have been listed in Schedule 6 of the SUSMP with reverse scheduling requirements.

Substance summary

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

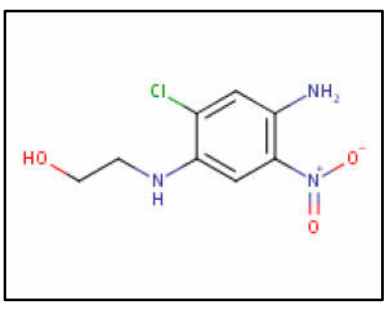

Figure 7. Structure of 2-chloro-5-nitro-*N*-hydroxyethyl *p*-phenylenediamine

Acute toxicity

The acute toxicity end-points for 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine are listed in the table below.

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Mice	2850	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	Guinea pig	Not irritating at 0.25 % concentration	N/A
Eye irritation	Guinea pig	Slightly irritating at 0.25 % concentration	Schedule 5
Skin sensitisation: QSAR prediction based on LLNA	N/A	Skin sensitiser (predicted EC3= 2.7)	Schedule 6

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

2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine has low acute oral toxicity in female CF1 mice. There are no data on acute dermal and inhalation toxicity.

Irritation

Only limited data are available in guinea pigs. 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine at a 0.25 % concentration is not irritating to the skin. The chemical at a 0.25 % concentration is slightly irritating to the eyes.

Sensitisation

Although the animal data (two limited quality non-guideline studies) indicate that the chemical is not a skin sensitiser, predictions from QSAR modelling indicated that the chemical was a moderate to strong skin sensitiser.

A 0.5 % solution of 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine (in 50 % ethanol) was administered as intracutaneous injections (0.1 mL) to the shaved skin of 15 female guinea pigs, twice/day, 6 days/week for three weeks. A control group of five female guinea pigs was used. After four weeks, the animals were challenged with an intracutaneous injection (0.1 mL) containing a 0.5 % solution of the chemical (in 50 % ethanol) at dilutions of 1:10, 1:100, 1:500 and 1:1000 in Ringer's solution. Severe erythema was observed 24 hours after challenge in both treated and control animals, which reduced to slight-well-defined erythema after 48 hours. 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine was reported to have 'shined through the skin' during the challenge phase, making it difficult to evaluate. However, this effect was not mentioned during the induction phase. The chemical was reported as non-sensitising (EC SCC, 2000).

In another study, guinea pigs (10/sex/dose) were induced with two intradermal injections (0.05 mL each); one containing Freund's complete adjuvant (FCA) (1:1 with distilled water) and the other containing a 3 % solution of 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine in water. The animals were then treated with a dermal application of 10 % sodium lauryl sulfate in white vaseline (unoccluded) on the following day. This was followed by (6–8 hours later) an occluded application (0.5 mL) of the chemical at 3 % in white vaseline. Forty-eight hours after the first induction, two intradermal injections (0.05 mL each) were given with 3 % of the chemical in FCA (diluted with 1:1

arachis oil). The animals were challenged 14 days later using a patch test (occluded for 24 hours) using 0.5 mL of 1, 2 or 3 % of the chemical in FCA (1:1 in arachis oil). No primary irritation or sensitisation was observed in the animals, either immediately after the challenge or 24 hours later, when compared with the control group (EC SCC, 2000). However, the EC SCC (2000) reported that the test protocol deviated from the OECD Test Guidelines for the Magnusson–Kligman test.

The sensitisation potency of 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine was predicted in a study on 229 hair dye substances using a QSAR model based on the local lymph node assay (LLNA). The study predicted the chemical to be a moderate to strong skin sensitiser, with an estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value of 2.7 (Sosted, 2004).

Skin sensitisation prediction using the OECD QSAR Toolbox v3.2 model was negative for the parent chemical—there were no protein binding alerts. However, of the nine possible chemical metabolites, three were predicted to be skin sensitisers. Potential protein binding reactions of the metabolites were Michael additions or Schiff Base formation.

Skin sensitisation prediction using OASIS–TIMES v2.27.14 (Optimized Approach based on Structural Indices Set-Tissue Metabolism Simulator) modelling was also negative for the parent chemical, although the model prediction was out of applicability domain, which indicates greater uncertainty about its reliability. The possible metabolites of the chemical, based on the metabolism simulators of OASIS–TIMES, were predicted to be strong skin sensitisers.

Repeat-dose toxicity

Based on a 90-day study in rats, 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine is not expected to cause serious damage to health from repeated oral exposure. Only limited data were available on repeated dose dermal toxicity and no data were available on repeated dose inhalation toxicity.

Genotoxicity

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

Carcinogenicity

Only limited animal data were available. Based on the available genotoxicity data, mitigating factors relating to the mechanisms of aromatic amine carcinogenicity and due to its chemical structure, this chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Only limited data were available and are not sufficient to derive a conclusion on reproductive or developmental toxicity of the chemical.

Public exposure

The chemical is reported to be used in permanent and semi-permanent hair dye preparations in Australia (NICNAS, 2007). Many countries, including those in the European Union, have banned the use of this chemical in cosmetics.

Currently, there are no restrictions in Australia on using this chemical in cosmetics. 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 under the identified uses.

International regulations

The chemical is listed on the following:

- EU Cosmetic Directive 76/768/EEC Annex II: 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;
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.
- EU Commission Directive 2007/54/EC: Amending Council Directive 76/768/EEC, concerning cosmetic products, for the purpose of adapting Annexes II and III thereto to technical progress.

Current scheduling status

2-Chloro-5-nitro-*N*-hydroxyethyl *p*-phenylenediamine is not specifically scheduled.

Scheduling history

2-Chloro-5-nitro-*N*-hydroxyethyl *p*-phenylenediamine has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. The submission had no objections to aligning the scheduling controls for this substance with the EU. It noted that 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine is listed in Annex II of the EU Cosmetics Regulations and cannot be used in cosmetics in the EU.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's questions, the Committee advised that the substance warrants control over use in cosmetics and hair dye products consistent with other similar hair dyes (specifically phenylenediamine entry in Schedule 6) on the basis of potential for skin sensitisation.

The committee advised that 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine does not require a separate schedule entry, as the substance was considered to be captured by the existing general entry for phenylenediamines in Schedule 6. However, the committee recommended inclusion of the substance in the index with cross reference to the general entry. This editorial change to the index will be made during the next update of the SUSMP.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: a) risk of skin sensitisation resulting from use as hair colourant; b) used in permanent and semi-permanent hair dyes in Australia and in concentrations of up to 2% and 1% overseas for oxidative and semi-permanent hair dyes, respectively. Many countries including EU have banned use in cosmetics; c) toxicity of the substance including predicted moderate to strong skin sensitisation potential from QSAR modelling; d) Labelling as per similar Schedule 6 chemicals used in oxidative hair colourant process; f) The committee noted the data was not sufficient to warrant consideration in a lower schedule.

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

2-Chloro-5-nitro-N-hydroxyethyl p-phenylenediamine is one of four oxidant hair dyes that were referred to the March 2016 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 the toxicity profile of 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine is consistent with other phenylenediamine-based hair dye ingredients and that it could be considered to be covered by the generic Schedule 6 listing for PHENYLENEDIAMINES. Accordingly, the only scheduling action proposed is to cross-reference 2-chloro-5-nitro-N-hydroxyethyl p-phenylenediamine in the index with the generic entry.

An implementation date is not relevant, since the substance is already covered by the generic PHENYLENEDIAMINES entry. The addition of the index cross-reference should be done at the earliest possible time.

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

Index - New Entry

2-CHLORO-5-NITRO-*N*-HYDROXYETHYL-*p*-PHENYLENEDIAMINE
cross reference: PHENYLENEDIAMINES

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

1.8 Bis-Isobutyl PEG/PPG

Referred Delegate's scheduling proposal

- In response to issues raised in a NICNAS New Chemical Assessments public report, the scheduling proposal is to create a new Schedule 6 entry for Bis-Isobutyl PEG/PPG-20/35/Amodimethicone Copolymer with appropriate exemption and cut-off to regulate its use in rinse-off cosmetic products.

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

Applicant's application and scheduling proposal

In December 2015, NICNAS under its New Chemicals assessment programme, referred the following proposal to be considered by the delegate:

- A proposal to create a new entry for Bis-Isobutyl PEG/PPG-20/35/Amodimethicone Copolymer in Schedule 6 when used in cosmetic products, except when used at low concentrations.

The reasons for the request are:

- Bis-Isobutyl PEG/PPG is an eye irritant, consistent with Schedule 6 factors.
- Bis-Isobutyl PEG/PPG is a skin irritant, consistent with Schedule 5 factors.

Similar to other surfactant chemicals previously considered for Scheduling, the key risk is the eye irritation, particularly when considered in the context of the use in hair care products.

The NICNAS risk assessment determined that there was no unreasonable risk to the public when used at 1% concentration in rinse-off hair care products (the maximum concentration proposed by the notifier). However, there remains uncertainty as to the actual concentration cut-off at which eye damage may occur, as eye irritation data was only available for a solution containing the polymer at 30-50% concentration.

Substance summary

Please refer to the New Chemical assessment report for Siloxanes and Silicones, 3-[(2-aminoethyl)amino]propyl Me, di-Me, hydroxy- and methoxy-terminated, polymers with polyethylene-polypropylene glycol bis(2-methyl-2-propen-1-yl) ether. This report is publicly available on the NICNAS website.

Acute toxicity

The toxicological investigations were conducted on the polymer at 30-50% concentration, unless stated otherwise. The acute toxicity end-points for bis-Isobutyl PEG/PPG-20/35/Amodimethicone Copolymer are listed in the below table.

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2,000	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	-
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Not provided	Not provided	-
Skin irritation	Rabbit	Slightly irritating (at 10% concentration)**	Schedule 5
Eye irritation	Rabbit	Severely irritating	Schedule 6
Skin sensitisation	Not provided	Not provided	-

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

**A 10% suspension of the product (containing the polymer at 30-50% concentration) was used as a test substance in the study.

Irritation

In a study conducted on rabbits the polymer at 30-50% was determined to be severely irritating to eyes, based primarily on conjunctival irritation, including effects which had not reversed by the end of the observation period.

A 10% suspension of the product (containing the polymer at 30-50% concentration) was found to be slightly irritating to the skin when tested on rabbits.

Repeat-dose toxicity

No information was provided.

Mutagenicity/genotoxicity

The polymer was not mutagenic in a bacterial reverse mutation study and it was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Carcinogenicity, reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

There will be repeated exposure of the public to the polymer (at up to 1% concentration) through the use as a surfactant in rinse off hair care products, such as shampoos and conditioners. The principal routes of exposure will be dermal, while ocular and oral exposures are also possible.

International regulations

No information was provided.

Current scheduling status

Bis-Isobutyl PEG/PPG is not specifically scheduled.

Scheduling history

Bis-Isobutyl PEG/PPG has not been previously considered for scheduling, therefore scheduling history is not available.

Pre-meeting public submissions

One public submission was received. The submission noted the substance is intended for use in dilute, rinse off cosmetic products. They agree the hazard profile merits scheduling consideration but questioned whether the risks require risk mitigation through scheduling and if they would deliver safety benefits for the end user. They believe use of first aid statement E1 "If in eyes wash out immediately with water." normally applied to severe eye irritants is redundant, because under the intended use situation (rinse-off cosmetic, e.g. shampoo or conditioner), if the product was to enter the eye, the user would instinctively wash the eye immediately under water. They note there are no restrictions on the use of this polymer internationally. They suggest that any scheduling restrictions should focus on uses that are not its current intended use to deter unintended uses, and allow this polymer to remain unscheduled when in rinse-off cosmetic preparations.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's questions, the Committee has advised that the toxicity of the substance warrants a Schedule 6 entry with an exemption for rinse off hair products below 1%, and entries in Appendix E and F.

The committee recommends that a new Schedule 6 entry be created Bis-Isobutyl PEG/PPG-20/35/Amodimethicone Copolymer as follows:

Schedule 6 - New Entry

BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER **except** in rinse-off hair products containing 1 per cent or less of bis-isobutyl PEG/PPG-20/35/amodimethicone copolymer.

Appendix E, Part 2 - New Entry

BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER.

Standard statements: A, E1.

Appendix F, Part 3 - New Entry

BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER.

Safety direction: 1 (avoid contact with eyes).

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) There are minimal risks to the user if the product containing the polymer is used as directed; b) The substance is used in rinse off cosmetics specifically shampoos and conditioners. It is widely used by the public and the hairdressing profession; c) The substance is a severe eye irritant consistent with schedule 6 criteria.

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, and accepts, ACCS advice that a new listing for this silicone copolymer be created in Schedule 6, with appropriate listings in Appendices E and F to require relevant label First Aid and Warning Statements. The preferred name for listing is the INCI name Bis-Isobutyl PEG/PPG-20/35/Amodimethicone Copolymer. While the acute toxicity profile is possibly consistent with SPF criteria for listing in Schedule 5, the delegate agrees that a primary listing in Schedule 6 is more appropriate, given the strong eye irritancy potential. The delegate agrees to include a specific exemption to the Schedule 6 entry only for use in rinse-off cosmetic products at concentrations of 1% or less.

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

The delegate has broadened the schedule entry recommended by the ACCS to include an exemption for all rinse-off cosmetic products, not just those used in preparations formulated for use on the hair.

The delegate notes the points raised in the industry submission, that scheduling does not achieve any useful risk mitigation because of the reduced potential for eye irritancy in dilute preparations and the lack of international controls over use in cosmetics. However, the delegate considers that the exemptions in the proposed Schedule 6 entry address these concerns and mandate appropriate labelling of products where the use pattern and higher concentrations that may be used could be associated with a higher potential for eye damage. The eye warning statement prescribed in Appendix F will only be applied to products that do not meet the Schedule 6 exemption.

The proposed implementation date is **1 June 2017**. A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

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 6 - New Entry

BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER **except** in rinse-off cosmetic products containing 1 per cent or less of bis-isobutyl PEG/PPG-20/35/amodimethicone copolymer.

Appendix E, Part 2 - New Entry

BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER.

Standard statements: A, E1.

Appendix F, Part 3 - New Entry

BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER.

Safety direction: 1.

Public submissions on the interim decision

One submission was received. The submission noted they do not believe the substance should be scheduled, but requested the proposed schedule entry be amended to exclude salts and derivatives to ensure no other substances are inadvertently captured. The submission also noted the risk profile of the substance was consistent with that of sodium lauryl sulfate and therefore any schedule entry should also be consistent with that entry. They questioned whether the substance could be considered a derivative according to the Poisons Standard definition, and noted a Cosmetic Ingredient Review grouped dimethicones and amodimethicones together. They also suggested the schedule entry reflect that of sodium lauryl sulfate entry for rinse-off products.

Delegate's final decision

The delegate notes the late submission received in response to the interim decision and has determined to defer a final decision to allow for further consideration of the issues raised in the submission received (above).

1.9 Propamocarb

Referred Delegate's scheduling proposal

- To delete the current Schedule 5 entry and create a new entry in Appendix B.

Applicant's application and scheduling proposal

In December 2015, the Australian Pesticides and Veterinary Medicines Authority (APVMA) referred the following proposal to be considered by the delegate:

- A proposal to reschedule propamocarb and remove it from Schedule 5 to be included in Appendix B.

The reasons for the request are:

- Propamocarb has low acute oral, dermal and inhalational toxicity;
- Propamocarb is not irritant to eyes or skin, but is a mild skin sensitiser;
- Propamocarb is not a teratogen, genotoxin or carcinogen;
- It belongs to the carbamate class of chemicals. However, unlike some other carbamates, acetylcholinesterase inhibition by propamocarb is seen only at very high dose levels, which are not achievable through dermal absorption and therefore this is considered not relevant to human risk assessment; and
- Decreased sperm count and motility observed in reproductive study were seen at dose levels which are unlikely to be achieved through dermal absorption or by inhalation in humans when the product is used in accordance with directions.

New data provided by the applicant includes:

- Acute toxicity studies;
- Skin irritation and sensitisation and eye irritation studies;
- Repeated dose toxicity studies in rats, rabbits and dogs;
- Reproduction and developmental toxicity studies in rats and rabbits;
- A comprehensive data package on *in vivo* and *in vitro* genotoxicity studies; and
- Neurotoxicity studies.

The majority of these studies were conducted after the ADI for propamocarb was set in 1987. The analysis of these new data supports the removal of propamocarb from Schedule 5 to an Appendix B listing in the Poisons Standard.

Substance summary

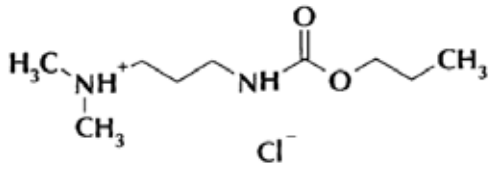

Figure 8. Structure of propamocarb (HCl salt)

Acute toxicity

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

Toxicity	Species	Result	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	SD Rat Wistar Rat	> 2000 > 5000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 5000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	5540	Low toxicity
Skin irritation	Rat	Non-irritant	Non-irritant
Eye irritation	Rabbit	Non-irritant	Non-irritant
Skin sensitisation (LLNA and maximisation)	Guinea pig	Sensitiser	Sensitiser

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

Repeat-dose toxicity

In the short-term toxicity studies, the critical effect was vacuolation of the choroid plexus in the brain and other tissues/glands, which was observed in a 28-day mouse dietary study at 172 mg/kg bw/d. The relevant short-term toxicity NOEL was set at the next lowest dose at 100 mg/kg bw/d.

In the sub-chronic toxicity studies, the critical effects observed were consistent with the effects found in the short-term studies. In rats reduced body weight gain and vacuolar changes in the choroid plexus and the lacrimal glands were observed. In dog dietary studies, wide spread vacuolation in secretary glands was observed and the sub-chronic NOEL was set at 131 mg/kg bw/d.

Consistent with the critical effects found in short-term and sub-chronic toxicity studies, vacuolation of multiple tissues was observed in 52-week dog dietary study. While vacuolation was seen at every dose level, there was a dose-related response in the severity of vacuolation. The NOEL for chronic toxicity was 39 mg/kg bw/d.

Genotoxicity

Propamocarb was not genotoxic in the battery of *in vivo* and *in vitro* genotoxicity studies.

Carcinogenicity

Propamocarb was not carcinogenic.

Reproduction and developmental toxicity

In the 2-generation reproductive toxicity study in rats, female survival was decreased in both generations, female fertility index was slightly lowered and in males, a decreased sperm motility and count was observed at the highest dose level tested (1000 mg/kg bw/d). Consistent with the findings in other rat toxicity studies, vacuolation of tissues was also observed at the higher dose levels. The NOEL for parental toxicity was set at 50 mg/kg bw/d. The NOEL of 200 mg/kg bw/d was set for pup development based on decreased pup viability at the highest dose. The overall NOEL for reproduction toxicity was set at 200 mg/kg bw/d based on the adverse effects on sperm parameters.

Propamocarb was not a teratogen in the tested animals. In rats, a reduced body weight gain and increased mortality of dams were the basis for a NOEL of 680 mg/kg bw/d for maternal toxicity. The NOEL for foetal toxicity was set at 204 mg/kg bw/d based on slightly increased number in foetal deaths and retarded ossification.

Neurotoxicity

Propamocarb was not acutely neurotoxic. In a sub-chronic study a vacuolation of choroid plexus in the ventricles of cerebrum and cerebellum was observed but these studies did not show any functional deficits in the tested animals and therefore the biological significance of vacuolation is unknown.

International regulations

Not explored by the APVMA in this report. Propamocarb is been registered for use in the USA and European Union.

Public exposure

No information was provided.

Current scheduling status

Propamocarb is currently listed in Schedule 5.

Scheduling history

Propamocarb has been considered for scheduling in May 1979 and July 1987. In the 1979 meeting the committee noted the limited toxicological data that were available but agreed to include the substance in Schedule 5 for the proposed, limited use (soil fungicide in ornamental plants).

In the 1987 meeting the committee considered additional studies and noted the low acute toxicity of the substance, that it was slightly irritating to the eye (rabbit) but non-irritating to the skin (rabbit). It did not cause skin sensitization (guinea pig), showed negative genotoxic, carcinogenic or teratogenic potential but was embryotoxic at maternotoxic doses. A schedule 5 entry was deemed appropriate.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

In response to the Delegate's questions the Committee advised that it was appropriate to retain the current listing for propamocarb in Schedule 5 due to concerns with the neurotoxicity in dogs and skin sensitisation potential, and therefore an Appendix B entry was not supported.

The committee advised that the current scheduling of propamocarb remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) toxicity of the substance: Acute oral toxicity (effects in dogs), skin sensitisation.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- APVMA Human Health Risk Assessment Report;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[9];

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

· Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that the current listing of propamocarb in Schedule 5 remains appropriate. The extension of the toxicological database provided in newly submitted studies confirms the relatively low toxicity of this fungicide, but the findings of slight skin sensitisation, neurotoxicity and lethality observed with acute oral dosing in dogs, and vacuolations observed in the brain and other tissues in chronic and repeat-dosing studies, albeit observed only at quite high dosing rates, nevertheless suggest that retaining the current listing in Schedule 5 is suitably precautionary.

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

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

1.10 Fluopicolide

Referred Delegate's scheduling proposal

· To consider whether fluopicolide requires listing in the Schedules.

Applicant's application and scheduling proposal

In December 2015, APVMA referred the following proposal to be considered by the delegate:

· A proposal to create a new entry in Appendix B for fluopicolide.

The reasons for the request are:

· Fluopicolide has very low acute oral, dermal and inhalational toxicity;

· Fluopicolide is not irritant to skin or a skin sensitiser;

· Fluopicolide is a slight eye irritant;

· Fluopicolide is not a teratogen, neurotoxin, reproductive toxin or genotoxin; and

· Benign liver tumours observed in an 18-month mouse study, were demonstrated in a supplementary studies to be most likely mouse specific, the mechanism of which was shown to be related to the induction of specific cytochrome P450s, which lead to liver tumours in mice specifically, and therefore these tumours were not relevant to the human risk assessment.

Substance summary

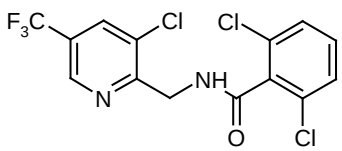

Figure 9. Chemicals structure of fluopicolide

Acute toxicity

The acute toxicity end-points for fluopicolide are listed in the following table.

Toxicity	Species	Results	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 5000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 5000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	5160	Low toxicity
Skin irritation	Rat	Non-irritant	Non-irritant
Eye irritation	Rabbit	Slight irritant	Slight irritant
Skin sensitisation	Guinea pig	Non-sensitiser	Non-sensitiser

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

Repeat-dose toxicity

In the short-term toxicity studies, the target/critical effect was liver pathology, which was observed in a 28-day dietary mouse study. The NOEL was set at 10.4 mg/kg bw/d based on increased liver weights associated with centrilobular hepatocellular hypertrophy at a LOEL (640 ppm).

In sub-chronic toxicity studies, critical effects were seen in the liver of rats. Histopathological effects observed in the 3-month rat dietary study included centrilobular hepatocellular hypertrophy in males at the LOEL (1400 ppm). An increase in the severity and incidence of trabecular hyperostosis of the bone joint was observed in females at the same dose level. A NOEL was set at 7.4 mg/kg bw/day (100 ppm).

Consistent with the liver pathology seen in the short-term and sub-chronic toxicity studies, liver pathology was the target organ in a chronic toxicity study in rats. A NOEL was set at 7.9 mg/kg bw/d (50 ppm) based on the increased absolute and relative liver weights associated with hepatocellular hypertrophy at the LOEL and highest does (400 and 3200 ppm, respectively). A markedly increased incidence of hepatocellular adenoma was observed at 3200 ppm.

Genotoxicity

Fluopicolide was not genotoxic based on a battery of *in vivo* and *in vitro* genotoxicity assays.

Carcinogenicity

Carcinogenicity studies showed an increased incidence of hepatocellular adenoma at the highest dose level (3200 ppm) in a 78-week mouse dietary study and a NOEL was set at 400 ppm. The incidence of hepatocellular carcinoma was unaffected by the treatment. Mechanistic studies demonstrated a mouse specific mechanism for the liver adenoma. It was concluded that the benign liver tumours observed in mice were not relevant to humans.

Reproduction and developmental toxicity

Fluopicolide was not a reproductive toxicant. A NOEL of 25.5 mg/kg bw/d for males and 32.9 mg/kg bw/d for females (500 ppm) was set based on increased liver and kidney weights, adverse kidney histopathology findings and reduced weight gains at the next highest dose tested. A reproduction NOEL of 103.4 mg/kg b/d (2000 ppm) was set at the highest dose tested in a 2-generation dietary study in rats.

Fluopicolide was not a teratogen in developmental studies in rats and rabbits. In rats, a NOEL for maternal and foetal toxicity was set at 60 mg/kg bw/d. This was based on reduced weight gain in dams and delayed development in foetuses observed at the dose level of 700 mg/kg bw/d. A NOEL for teratogenesis was set at the highest dose level 1000 mg/kg bw/day. In rabbits, fluopicolide killed the majority of the dams and their pups at the highest dose tested (60 mg/kg bw/d). At this dose level, a high level of premature delivery, body weight loss and decreases in food consumption were observed. The NOEL for maternal and foetal toxicity was 20 mg/kg bw/d and the NOEL for foetal development was 60 mg/kg bw/d.

Neurotoxicity

Neurotoxicity studies conducted in rats demonstrated that fluopicolide was not neurotoxic.

Public exposure

No information was provided.

International regulations

Not explored by the APVMA in this report. Fluopicolide has been approved for use in the European Union since 2006.

Current scheduling status

Fluopicolide is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

In response to the Delegate's request the Committee has advised that the toxicity profile of fluopicolide is sufficiently low to support it being included in Appendix B. The Committee noted the slight and transient eye irritation effects of the substance.

The committee advised the following amendments to the Poisons Standard:

Appendix B, Part 3 - New Entry

FLUOPICOLIDE

Part 1 - Reasons for Entry - a) low toxicity.

Part 2 - Area of Use - 1.3.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) Toxicity of the substance - Slight and transient eye irritation effects.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- APVMA Human Health Risk Assessment Report;
- ACCS advice;

- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[10];
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts, the ACCS advice that the toxicity profile of fluopicolide is not consistent with SPF criteria for listing in any of the schedules. Accordingly, the delegate proposes to list fluopicolide in Appendix B, to designate that it has at least been considered for scheduling.

The proposed implementation date is **1 October 2016**. Since listing in Appendix B is **not** equivalent to a decision to list a substance in a **schedule**, an implementation date is not strictly relevant. However, early advice to the APVMA of this decision will facilitate prompt registration of products under consideration by the APVMA. Accordingly, amendment of Appendix B at the earliest revision of the Poisons Standard is recommended.

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

Appendix B, Part 3 - New Entry

FLUOPICOLIDE.

Part 1 - Reasons for Entry - a) low toxicity.

Part 2 - Area of Use - 1.3

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

1.11 Nonanoic acid

Referred Delegate's scheduling proposal

- To create a new Schedule 5 entry for the use of NONANOIC ACID in agricultural preparations with a proposed exemption concentration cut-off at 3%.

Applicant's application and scheduling proposal

In December 2015 the APVMA referred the following proposal to be considered by the delegate:

- A proposal to create a new entry for nonanoic acid (NNA) in Schedule 5 with a 5% cut-off.

The reasons for the request were:

- NNA has low systemic toxicity and is not corrosive. The acute oral and dermal toxicity (rat) is greater than 2000 mg/kg. Acute inhalation LC_{50} (rat) is more than 3000 mg/m^3 (4 h).

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

- The human clinical data for skin irritation indicates reversible moderate irritation. Eye irritation is slight to moderate and NNA is not classifiable as a skin sensitiser. The eye irritation is considered reversible although corneal opacity has been reported in some older studies.
- NNA did not cause marked organ toxicity in repeat dose toxicity studies, but caused gastrointestinal irritation. It is unlikely to produce significant toxicity (organ damage, respiratory sensitisation, mutagenicity, carcinogenicity, reproductive toxicity).
- The evaluation considered whether the eye irritation observed and the uncertainty in the data available was sufficient to classify NNA as an irreversible eye irritant (Schedule 6). Recent studies for octanoic acid and decanoic acid (*in vivo* eye irritation GLP test according to OECD TG 403 and a Bovine Corneal Opacity and Permeability (BCOP) test respectively) showed evidence for reversible eye irritation. On this basis Schedule 5 was recommended.
- A low level cut-off of 5% is also proposed for the schedule 5 listing given that the endpoint is a local effect. A threshold for moderate irritation (i.e. the threshold for GHS hazard classification is greater than 10%). At approximately 10% mild irritation is expected and at 3% very slight irritation has been noted in clinical patch tests. A threshold for slight to moderate irritation is interpolated as 5%.

The evaluation also considered that other medium chain fatty acids and their derivatives are not listed as scheduled poisons.

Substance summary

Please refer to publically available reports on nonanoic acid (potassium salt) on NICNAS website for nonanoic acid, at: http://www.nicnas.gov.au/__data/assets/pdf_file/0009/10341/SN2FR.pdf and https://www.nicnas.gov.au/__data/assets/word_doc/0007/19789/NA114FR.docx.

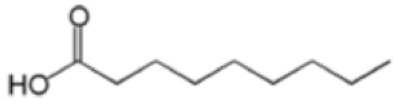

Figure 10. Structure of nonanoic acid

Nonanoic acid (NNA; also frequently referred to as pelargonic acid) is a naturally occurring carboxylic acid with a carbon chain-length of nine, belonging to the chemical class saturated fatty acids commonly referred to as medium chain fatty acids (C8 to C12).

It is a clear, colourless liquid with a weak odour. NNA is soluble in aqueous solution however it can readily form esters and partially dissociate into the pelargonate anion ($CH_3(CH_2)_7COO^-$) and the hydronium cation (H_3O^+) in an aqueous solution (NICNAS IMAP, 2015). The molecular weight (158.24 g/mol) and octanol-water partition coefficient (3.4 $\log P_{ow}$) of NNA suggest that dermal penetration is possible.

Oral, dermal or inhalation absorption studies are not available. The default of 100% is assumed for oral, dermal and inhalation absorption. NNA has low systemic toxicity and is not corrosive. The acute oral and dermal toxicity (rat) is greater than 2000 mg/kg. Acute inhalation median lethal concentration (LC_{50})(rat) is more than 3000 mg/m^3 (4 h).

The human clinical data for skin irritation indicates reversible moderate irritation. Eye irritation is slight to moderate and nonanoic acid is not classifiable as a skin sensitiser. The eye irritation is considered reversible although corneal opacity has been reported in some older rabbit studies. NNA did not cause marked organ toxicity in repeat dose toxicity studies. It did cause gastrointestinal irritation. It is unlikely to produce significant toxicity (organ damage, respiratory sensitisation, mutagenicity, carcinogenicity, reproductive toxicity).

For occupational margin of exposure assessment the selected no observed adverse effect level (NOAEL) is from a 28-day oral study in male and female Wistar rats. NNA was administered by gavage at doses of 0, 50, 150 or 1000 mg/kg bw/d in concentrations of 1, 3 or 20% in propylene glycol as a

vehicle. Treatment related effects were minimal except for gastrointestinal irritation. An irregular surface of the forestomach was noted in all high dose animals. In this dose group, histopathological examination showed slight to marked hyperplasia of the squamous epithelium of the forestomach. These latter effects were also noticed in 2 from 10 animals of the mid-dose group but these were considered to be without any toxicological relevance since they were minimal and occurred in the absence of (other) functional or morphological disturbances or clinical signs. Therefore a local oral (i.e. for gastric effect) NOAEL of 150 mg/kg bw/d was established (ECHA 2013). The ECHA did not establish a systemic NOAEL.

Given the effects are local and not systemic for home garden assessments the potential for skin and eye contact and the magnitude of skin and eye irritation should be the focus. The threshold for slight to moderate skin irritation is between 3 and 10% w/w NNA. At 10% skin irritation is transient and mild.

For occupational margin of exposure assessment the selected NOAEL is from a 28-day oral study in Wistar rats (ECHA 2013). A local irritation effect was noted, with an oral NOAEL of 150 mg/kg bw/d; general systemic toxicity was not observed. The NOAEL is based on slight to marked hyperplasia of the squamous epithelium of the forestomach, a local irritant effect rather than a systemic effect. In this case the presence or absence of skin and eye irritation is the primary considerations for the home garden health risk assessment but also for occupational risk assessment.

Based on skin and eye irritation the evaluation proposes that NNA be included in Schedule 5 of the SUSMP with a cut off of 3%.

Hazard characterisation summary

The following table summarises the toxicological information for nonanoic acid.

Study type	Species / Test System	Result	Reference
Acute Oral Toxicity	Wistar rat, Crl:(WI) BR (outbred, SPFQuality), 3/sex/dose	LD_{50} >2000 mg/kg bw	ECHA 2013
Acute Dermal Toxicity	Wistar rat, Crl:(WI) BR (outbred, SPFQuality), 5/sex/dose	LD_{50} >2000 mg/kg bw	ECHA 2013
Acute Inhalation Toxicity	Details not provided in summary	LC_{50} (4 h) >5.3 mg/L	ECHA 2013
Skin irritation	Human and Rabbits (NZW)	Irritating	ECHA 2013
Eye irritation	Human experience and Rabbits (NZW)	Irritating	ECHA 2013a, b, c
Skin sensitisation	Albino Guinea pigs, Dunkin Hartley strain (SPF-quality), 10 females per test item group. Maximisation test.	No evidence of sensitisation	ECHA 2013
Respiratory sensitisation	No information	No evidence of sensitisation	ECHA 2013
Carcinogenicity	Non-standard dermal carcinogenicity study	No evidence for carcinogenicity	ECHA 2013
Mutagenicity – Genetic toxicity	Bacterial gene mutation test, mammalian *in vitro* chromosomal aberration test and *in vivo* mouse	No evidence for genotoxicity or mutagenicity	ECHA 2013

	micronucleus assay		
Toxicity to reproduction – fertility Toxicity to reproduction – development Toxicity to reproduction – breastfed babies. Effects on or via lactation	47 week Rat, McCollum-Wisconsin. A casein diet, containing 18.5% medium chain triglyceride (MCT) The MCT contained about 51% octanoic acid and 35% decanoic acid resulting in an octanoic acid dietary dose of about 4700 mg/kg bw/d and a decanoic acid dietary dose of about 3200 mg/kg bw/d.	No concern for reproductive toxicity. Overall LOEL of ≥ 8000 mg/kg bw d	ECHA 2013
Specific Target Organ Toxicity – Repeat Dose	28 day study with Wistar rat, Crl:(WI) BR (outbred, SPF-Quality), 5 males and 5 females per dose group	NOAEL – 150 mg/kg bw/d Based on the observation of macroscopic irregular surface of the forestomach (hyperplasia of the squamous epithelium) at 1000 mg/kg bw/d	ECHA 2013

Public exposure

The technical report notes that NNA was listed on the 2007 OECD list of high production volume chemicals, meaning that the chemical was produced or imported levels greater than 1,000 tonnes per year in at least one member country/region (OECD 2007).

The principal uses for NNA are in cosmetics and conventional pesticides. NNA is used in cosmetics for skin-conditioning, fragrance, surfactant-cleansing, and surfactant-emulsifying (Johnson et al., 2011). It is an active ingredient of antimicrobial agents (e.g. surface sanitiser), blossom thinners (formulations that decrease flower load and improve fruit yields), biopesticides and conventional pesticides registered with the US Environmental Protection Agency (US EPA) (US EPA, 2010, US EPA, 2000). The US EPA-registered products contain NNA in the range 0.96-57%. It is also used in lacquers, plastics, lubricants, metalworking fluids, photographic plate development and in the manufacture of plastics and pharmaceuticals (US EPA, 2010). In Australia NNA has reported domestic use as a surface-active agent (NICNAS IMAP, 2015).

Fatty acids are a significant part of a person's normal daily diet with NNA being naturally present in fruits, vegetables, dairy products, meat and grains at levels ranging from 0.2 - 400 mg/kg (Marin Water, 2010). Natural levels of NNA include 1.4 mg/kg in dried mushrooms, 0.03-0.04 mg/kg in beer, and 2.5-20.5 mg/kg in coffee (Council of Europe, 2000).

International regulations

The APVMA report notes that no known Australian or international restrictions were identified in their review or by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS IMAP, 2015).

The FDA has approved NNA for use as a direct food additive under the synthetic flavouring substances and adjuvants category at the minimum quantity required to produce their intended effect (21CFR172,

2015), and as an indirect additive as a surface sterilant on food-processing equipment and utensils and dairy-processing equipment (21CFR178, 2015), at the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food. FDA approval has also been reported for use in cosmetics, shampoos and other personal care products and in transdermal drug delivery systems (US EPA, 2010).

It was also noted the primary metabolite of NNA is azelaic acid, which is approved by the Therapeutic Goods Administration as an over the counter acne treatment.

Current scheduling status

Nonanoic acid is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

Two public submissions were received. The first submission did not support the scheduling proposal. It was claimed that at the concentration of the ready-to-use product, the pH was sufficiently low to not require scheduling. A cut off concentration of 4% was suggested. The second submission did not support the proposal. They noted the substance is listed in the ARTG ingredient list and may have a use as an excipient in fragrances. Therefore, they request that the ACCS considers exemption for the use of the substance as an excipient in therapeutic goods, with a suitable cut off concentration if appropriate.

The public submissions are available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the Committee have advised that the irritant properties of the substance meet the criteria for inclusion in Schedule 6 rather than Schedule 5. In relation to the Delegate's questions, the Committee noted the broad use pattern of NNA and given its irritancy, the schedule entry should not be restricted to agricultural uses only to capture other areas of potential public exposure.

The Committee advised that a 10% cut off for the substance was appropriate, below which the substance would not be scheduled. This cut off concentration was considered appropriate to avoid capturing its use in food additives and cosmetics.

The Committee recommended use of the IUPAC name of nonanoic acid for scheduling, and the following amendments to the Poisons Standard:

Schedule 6 - New Entry

NONANOIC ACID **except** in preparations containing 10 per cent or less of nonanoic acid.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) The substance has severe eye irritation potential that meet Schedule 6 criteria; f) The committee considered the eye irritancy/damage of the substance warranted schedule 6 entry. It was noted currently available products (non-agricultural) would be below 10%.

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.

Delegate's interim decision

Nonanoic acid was referred by the APVMA for consideration of scheduling because if its use as an adjuvant in AgVet products. This substance is a naturally occurring fatty acid and it may also be used as a food additive and in therapeutic goods. As such, it represents a challenge to devise a scheduling proposal that provides appropriate controls over uses where suitable warning statements are necessary, while exempting uses where such controls are inappropriate.

The delegate notes the advice from the ACCS, that a new Schedule 6 entry be created for nonanoic acid, with a cut-off to exempt in preparations containing 10% or less. The advice for a primary listing in Schedule 6 is based primarily on the potential for severe eye damage associated with exposure to this fatty acid, while most of the other toxicological criteria are consistent with SPF criteria for listing in Schedule 5. The delegate notes comments made by the ACCS that the evaluation of the eye irritancy studies presented lacked rigour and that there is some uncertainty about the severity and reversibility of the lesions associated with concentrated solutions of the acid. The delegate also notes submissions from industry, suggesting the lack of concern for dilute preparations and that the ACCS did not recommend any entries in Appendices E or F, to provide for any First Aid or label Warning Statements for products that would be captured by the schedule listing.

The delegate has decided to create a primary listing for nonanoic acid (the preferred IUPAC name) in Schedule 5, with an exemption for products containing 10% or less. There is sufficient evidence that, at concentrations below 10%, that should cover most uses and natural occurrences of nonanoic acid in products available to the public, the risks of eye damage are sufficiently ameliorated to warrant scheduling controls unnecessary.

The proposed implementation date is **1 February 2017**. While an early implementation date would facilitate registration of new products by the APVMA, there is some doubt as to whether any existing products regulated by the APVMA could be affected and require re-labelling. Accordingly, an intermediate implementation date is proposed.

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.

Schedule5 - New Entry

NONANOIC ACID **except** in preparations containing 10 per cent or less of nonanoic acid.

The delegate has determined that listing in Schedule 5 is more consistent with SPF criteria and provides adequate controls for any preparations in current use that would contain more than 10% of nonanoic acid.

Public submissions on the interim decision

No submissions were received.

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

Delegate's final decision

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

The implementation date is 1 February 2017.

1.12 Di-Bak Parkinsonia

Referred Delegate's scheduling proposal

- To consider the need for scheduling a new biological pesticide containing three fungal strains, *Lasiodiplodia pseudotheobromae* (strain NT039), *Neoscytalidium novaehollandiae* (strain QLD003), and *Macrophomina phaseolina* (strain NT094).

Applicant's application and scheduling proposal

In December 2015, the OCS, based on an application made to the APVMA to approve three new biological active constituents, requested that the Delegate consider creating new entries for *Lasiodiplodia pseudotheobromae (strain NT039), Neoscytalidium novaehollandiae (strain QLD003)* and *Macrophomina phaseolina (strain NT094)* in Schedule 5 of the SUSMP with cut off exemptions. The proposed new entries are as follows:

- *Lasiodiplodia pseudotheobromae* (*strain NT039)* except when used in capsule preparations at a concentration of 16 CFU/dosage unit or less;
- *Neoscytalidium novaehollandiae (strain QLD003)* except when used in capsule preparations at a concentration of 16 CFU/dosage unit or less;
- *Macrophomina phaseolina (strain NT094)* except when used in capsule preparations at a concentration of 16 CFU/dosage unit or less.

The reasons for the request are:

- Available literature on human clinical case studies suggests that human infection (where reported) is generally opportunistic, although instances of infection in the absence of identifiable injury or immunocompromised state have been described.
- Acute intraperitoneal sighting studies in rat show evidence of infectivity by all the active constituents individually. Pathogenicity could not be definitively determined from these studies, though under the study conditions pathogenicity was considered unlikely.
- Acute intraperitoneal and oral toxicity/pathogenicity studies with the product did not show evidence of infectivity; however, these studies have reduced regulatory value due to deviations from the test guidelines. Pathogenicity could not be definitively determined from these studies, though under the study conditions pathogenicity was considered unlikely.
- The skin sensitisation study (by local lymph node assay) did not indicate a skin sensitisation potential for *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae* or *Macrophomina phaseolina*; however, this study has limited regulatory value due to lack of verification of the test item extraction method.
- No acute inhalational or dermal toxicity or skin or eye irritation studies were submitted. Cases of severe sinus and eye infection by *Lasiodiplodia pseudotheobromae* in humans have been recorded in the academic literature, where no obvious mode of acquisition or underlying medical condition was present. The number of reported case studies internationally demonstrates a low rate of infection. Given the information provided, the risks associated with exposure to the constituent fungi in the proposed product is considered by the OCS to be low, though the potential for minor human pathogenicity by the active constituents cannot be ruled out.

- Repeat-dose studies were not undertaken; however it is considered that the proposed formulation and intended use pattern of the product present a low potential for the active constituents to cause harm.
- The carcinogenicity, genotoxicity and immunotoxicity potential of *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae and Macrophomina phaseolina* cannot be determined at this time.
- The OCS considers that the likelihood of infectivity/pathogenicity associated with the use of the active constituents and product can be mitigated through appropriate label warnings, as indicated in the proposed safety directions ("Avoid contact with the eyes and skin", "When using the product wear elbow-length chemical resistant gloves" and "Wash hands after use") and precautionary statements ("Avoid direct contact with the contents of capsules" and "Not for food-producing use").

Consideration of the SPF criteria and application of the cascading principles outlined in the SPF indicates that the biological active constituents *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae and Macrophomina phaseolina* meet the scheduling factors for a Schedule 5 listing in the SUSMP with an exemption cut off (to unscheduled) for the product when used in capsule preparations containing 16 CFU/dosage unit or less, based on the active constituents presenting a low health hazard and the intended product use pattern and formulation minimising the potential for the active constituents to cause harm.

Substance summary

Di-Bak Parkinsonia is a new biological herbicide consisting of three fungal species – *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae* and *Macrophomina phaseolina* – combined with a millet substrate in gelatine capsule formulation.

Acute toxicity - product

The acute toxicity end-points for Di-Bak Parkinsonia are listed below.

Toxicity	Species	Result	SPF* Classification
Acute intraperitoneal toxicity/pathogenicity LD_{50}	Rat	> 16 CFU/strain/animal^	N/A
"Acute" oral toxicity LD_{50} (mg/kg bw)^	Rat	> 2g/kg bw/d^	[Unscheduled]
Acute dermal toxicity LD_{50} (mg/kg bw)	n/a		
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	n/a		
Skin irritation	n/a		
Eye irritation	n/a		
Skin sensitisation LLNA^	Mice	Unlikely to be a skin sensitiser^	[Unscheduled]

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

^ Study has reduced regulatory value

Repeat-dose toxicity

Repeat-dose studies were not undertaken; however it is considered that the proposed formulation and intended use pattern of the product present a low potential for the active constituents to cause harm.

Reproduction and developmental toxicity, neurotoxicity and genotoxicity

No information was provided.

Observations in humans

Mycoses by *M. phaseolina* and *L. pseudotheobromae* appear generally to be cutaneous or subcutaneous in nature and often follow some sort of trauma or injury. However, cases of severe eye and sinus infection by *L. pseudotheobromae* in humans have been recorded in the academic literature where no obvious mode of acquisition or underlying medical condition was present.

Public exposure

No information was provided.

No domestic (general public) exposure is expected for *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae* and *Macrophomina phaseolina*. The intended use of Di-Bak Parkinsonia Bioherbicide is as a bioherbicide for *Parkinsonia aculeata* trees present in grazing land. The OCS notes that *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae* and *Macrophomina phaseolina* fungal species are already present in trees native to Australia.

International regulations

No information was provided.

Current scheduling status

Di-Bak Parkinsonia Bioherbicide or its component fungal species are not specifically scheduled.

Scheduling history

Di-Bak Parkinsonia Bioherbicide or its component fungal strains have not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the Committee has advised that the product warrants inclusion in Schedule 5 due to infectivity potential, despite exposure risks being minimal due to the formulation presentation and the presence of the fungi in the natural environment. It was noted the fungi are present in concentrated form and thus increases the risks. The Committee advised that warning statements recommended for inclusion under APVMA registration requirements would sufficiently ameliorate risks.

The committee advocated for new Schedule 5 entries be created for *Lasiodiplodia pseudotheobromae, Neoscytalidium novaehollandiae* and *Macrophomina phaseolina* with appropriate exemptions and cut off as follows:

Schedule 5 - New Entries

LASIODIPLODIA PSEUDOTHEOBROMAE **except** when used in capsule preparations at a concentration of 16 CFU or less per capsule.

NEOSCYTALIDIUM NOVAEHOLLANDIAE **except** when used in capsule preparations at a concentration of 16 CFU or less per capsule.

MACROPHOMINA PHASEOLINA **except** when used in capsule preparations at a concentration of 16 CFU or less per capsule.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) Potential for the substance to be infective in some individuals; d) the presentation of the active ingredient in capsule form sufficiently reduces exposure to the extent that scheduling is not required if in capsules and labelled in accordance with APVMA labelling requirements.

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 the three fungal spores contained in the referred biological herbicide product be listed in Schedule 5, with an exemption cut-off at 16CFU or less in an encapsulated dose form. The delegate notes that this advice is primarily based on the potential infectivity to humans of these naturally-occurring fungi, and that there is no specific SPF guidance on the use of infectivity and/or pathogenicity data in making a scheduling decision. It was also noted that the proposed method of use (insertion of capsules into holes bored in trees) further reduces the risk of exposure to the public, and justifies exempting the specific product from the schedule entry. While these proposals would lead to the scheduling capture of any other product formulated with these three fungi, it is not envisaged that the natural occurrence of any of these fungal strains in the environment would be captured by the schedule entry.

The delegate thinks it necessary to further specify the type of agricultural use as a herbicide, as well as specifying the encapsulated nature of the product, in the schedule entry.

The proposed implementation date is **1 October 2016**. An early implementation for this scheduling proposal will facilitate registration of the product by the APVMA.

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

Schedule 5 - New Entries

LASIODIPLODIA PSEUDOTHEOBROMAE **except** when used as a herbicide in capsule preparations at a concentration of 16 CFU or less per capsule.

NEOSCYTALIDIUM NOVAEHOLLANDIAE **except** when used as a herbicide in capsule preparations at a concentration of 16 CFU or less per capsule.

MACROPHOMINA PHASEOLINA **except** when used as a herbicide in capsule preparations at a concentration of 16 CFU or less per capsule.

Public submissions on the interim decision

No submissions were received.

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

Delegate's final decision

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

The implementation date is 1 October 2016.

1.13 Streptomyces lydicus

Delegate's scheduling proposal

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

- To create a new Schedule 6 entry for *Streptomyces lydicus* WYEC 108 for agricultural use, with an exemption for preparations containing 0.037% or less.

Applicant's application and scheduling proposal

In December 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 *Streptomyces lydicus* WYEC 108 as a new active constituent and the registration of a product, Actinovate BioFungicide, containing *Streptomyces lydicus* WYEC 108, recommends that the delegate consider creating a new entry for *Streptomyces lydicus* WYEC 108 in Schedule 6 of the SUSMP with cut-off exemptions (to unscheduled) when used in preparations containing 0.037 per cent or less of *Streptomyces lydicus* WYEC 108 for agricultural use.

The reasons for the request are:

- The OCS assessment estimated *Streptomyces lydicus* WYEC 108 to be a potential skin and respiratory sensitiser, therefore meeting the Scheduling Policy Framework criteria for Schedule 6.
- The OCS assessment concluded that the product Actinovate BioFungicide containing 0.037% (w/w) *Streptomyces lydicus* WYEC 108 did not meet the Scheduling Policy Framework criteria, and as such, an exemption cut-off was proposed at 0.037 per cent or less for agricultural use.

Substance summary

Acute toxicity

The acute toxicity end-points for *Streptomyces lydicus* WYEC 108 are listed below.

Toxicity	Species	Results	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>5050 (~ 2.5 x 10^9 CFU/kg bw) No deaths	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5050 (~ 9.95 x 10^9 CFU/kg bw) No deaths	N/A
Acute inhalation toxicity	Estimated	Low	N/A
Acute pulmonary toxicity/pathogenicity	Rat	LD_{50} > 9.1 x 10^8 CFU/rat No deaths Not a pulmonary toxicant/pathogen	N/A

Acute intravenous injection toxicity/pathogenicity	Rat	LD_{50} > 9.33 x 10^8 CFU/rat No deaths Non-toxic/Non-pathogenic	N/A
Skin irritation	Rabbit	Non-irritant	N/A
Eye irritation	Rabbit	Slight eye irritant	N/A
Skin and respiratory sensitisation	Estimated	Potential sensitiser	Schedule 6

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

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

Toxicity	Species	Results	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat (F only)	LD_{50} >5000 No deaths	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} >5050 1 death	N/A
Acute inhalation toxicity	Estimated	Low	N/A
Skin irritation	Rabbit	Non-irritant	N/A
Eye irritation	Rabbit	Non-irritant	N/A
Skin and respiratory sensitisation	Estimated	Non-sensitising	N/A

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

Other toxicity data

In a pulmonary toxicity/pathogenicity and infectivity study, no mortalities were observed in rats following intra-tracheal injection at dose of 9.1 x 10^8 CFU of *Streptomyces lydicus* strain WYEC 108 per animal. No treatment-related signs of toxicity were observed. The microbial pest control agent (MPCA) was detected in the kidney, liver, mesenteric lymph nodes and in the lungs of treatment test animals up to Day 21, but had cleared by Day 28 or earlier. *Streptomyces lydicus* WYEC 108 was not considered to be toxic/pathogenic when administered *via* intra-tracheal injection to rats at 9.1 x 10^8 CFU/animal.

In an intravenous injection infectivity study, no mortalities or significant signs of toxicity were observed in rats following injection with *Streptomyces lydicus* WYEC 108 at 9.33 x 10^8 CFU per animal. *Streptomyces lydicus* WYEC 108 was detected in the blood, brain, kidney, mesenteric lymph nodes, lungs, liver and spleen up to Day 21, but cleared from all test animals by Day 28 or earlier. *Streptomyces lydicus* WYEC 108 was not considered to be toxic/pathogenic when administered *via* intravenous injection to rats at 9.33 x 10^8 CFU/animal.

Acute inhalation toxicity on *Streptomyces lydicus* WYEC 108 was not provided. Extrapolating from the pulmonary toxicity/pathogenicity and infectivity study, the OCS considered that *Streptomyces lydicus* WYEC 108 was a low acute inhalation toxicant in rats as no treatment-related effects were observed. However, the study was not suitable to establish an acute inhalational LC_{50}.

Observation in humans

No information was provided.

Public exposure

At this time, the proposed agricultural use of *Streptomyces lydicus* WYEC 108 is not expected to result in general public exposure. Spray drift considerations have not been considered.

International regulations

Products similar to, and containing *Streptomyces lydicus* WYEC 108 at the same concentration as Actinovate BioFungicide, are available in the USA, Canada and New Zealand.

Current scheduling status

Streptomyces lydicus strain WYEC 108 is not specifically scheduled. Dihydrostreptomycin and streptomycin are both listed in Schedule 4 of the Poisons Standard.

Scheduling history

Streptomyces lydicus strain WYEC 108 has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the Committee have advised that there is insufficient evidence of skin and respiratory sensitisation potential to warrant inclusion of the substance in Schedule 6, and advocated for the substance to be included in Appendix B.

The committee recommended the following amendments to the Poisons Standard:

Appendix B, Part 3 - New Entry

STREPTOMYCES LYDICUS WYEC 108.

Part 1 - Reasons for Entry - a) low toxicity.

Part 2 - Area of Use - 1.3 - Fungicide

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: a) low risk of adverse effects compatible with Appendix B; b) to be used in the agricultural setting, as a fungicide and soil supplement; c) Low toxicity and infectivity potential; d) Product to be used in agricultural and industrial setting.

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[13];
- Other relevant information.

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

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that this biofungicidal preparation, containing the bacterium *Streptomyces lydicus* strain WYEC 108, does not satisfy any of the SPF criteria for listing in the schedules and should be listed in Appendix B. It is noted that the evidence for potential skin sensitisation and irritancy was considered by the ACCS to be insufficient to warrant scheduling, and that no other toxicity, infectivity or pathogenicity was apparent from the studies presented.

The proposed implementation date is **1 October 2016**. Since listing in Appendix B is **not** equivalent to a decision to list a substance in a **schedule**, an implementation date is not strictly relevant. However, early advice to the APVMA of this decision will facilitate prompt registration of products under consideration by the APVMA. Accordingly, amendment of Appendix B at the earliest revision of the Poisons Standard is recommended.

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.

Appendix B, Part 3 - New Entry

STREPTOMYCES LYDICUS WYEC 108

Part 1 - Reasons for Entry - a) low toxicity

Part 2 - Area of Use - 1.3 - Fungicide

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

1.14 Isopyrazam

Referred Delegate's scheduling proposal

· The scheduling proposal is to create a new Schedule 6 entry for isopyrazam.

Applicant's application and scheduling proposal

In December 2015, the OCS has referred the following scheduling proposal to be considered by the delegate:

· A proposal to create a new entry for Isopyrazam in Schedule 6 of the SUSMP, with no exemption cut off.

The reasons for the request were:

· The APVMA have received an application for approval of the new active constituent isopyrazam, a carboxamide broad-spectrum foliar fungicide with an inhibitory mode of action on the enzyme succinate dehydrogenase (complex II) within the fungal mitochondrial respiration chain.

· Isopyrazam is a skin sensitiser in a local lymph node assay (LLNA) and a slight eye irritant in rabbits.

· Isopyrazam has a low acute oral toxicity with $LD_{50} \leq 2000$ mg/kg bw in rats.

Substance summary

Isopyrazam is a new carboxamide broad-spectrum foliar fungicide with an inhibitory mode of action on the enzyme succinate dehydrogenase (complex II) within the fungal mitochondrial respiration chain. The proposed product is intended for the control of black spot (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) in apples, and for control of black spot (*Venturia pirina*) in pears. Isopyrazam contains two diastereoisomers, designated syn and anti-isomers. Both of the isomers are biologically active.

The European Food Safety Authority has also published a report on the risk assessment for isopyrazam.

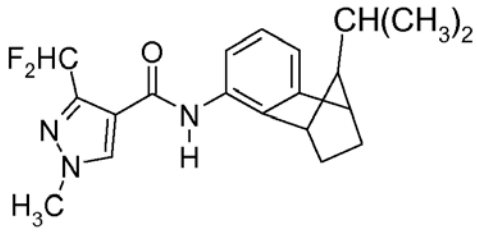

Figure 11. Structure of Isopyrazam

The majority of metabolism and toxicology studies submitted were performed with syn:anti material with a ratio of around 93:7, but there were also a number of studies performed with material with an isomeric ratio of around 70:30 and a number of comparative studies where the test materials ranged from 100% syn through to 100% anti-isomer to help determine if the isomeric ratio had an influence on the mammalian toxicity of the test material.

Acute toxicity

The acute toxicity end-points for isopyrazam are listed in the following table.

Toxicity	Species	Results	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	$550 > LD_{50} \leq 2000$	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	$LD_{50} > 5000$	Appendix B
Acute inhalational toxicity LC_{50} (mg/m³/4h)	Rat	$LD_{50} > 5000$	Appendix B
Skin irritation	Rabbit	Non irritant	Appendix B
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (LLNA)	Mouse	Sensitiser	Schedule 6

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

The acute toxicity end-points for Seguris Flexi (containing 12.5% isopyrazam) are listed in the table below.

Toxicity	Species	Results	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1750	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} > 5000	Appendix B
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	LD_{50} > 2710 (no deaths)	Appendix B
Skin irritation	Rabbit	Moderate irritant	Schedule 5
Eye irritation	Rabbit	Severe irritant	Schedule 6
Skin sensitisation (LLNA)	Mouse	Non-sensitiser	Appendix B

Isopyrazam active constituent was found to be of low acute oral toxicity (550 < LD_{50} < 2000 mg/kg bw), low acute dermal toxicity (LD_{50} > 5000 mg/kg bw) and low acute inhalational toxicity (LC_{50} > 5280 $mg/m^3/4h$).

Irritation

Isopyrazam was found to be a slight irritant to the eye, and non-irritating to skin in rat studies.

Sensitization

Isopyrazam was found to be a sensitiser in local lymph node assay in mice.

Repeat-dose toxicity

The systemic toxicity of isopyrazam in oral studies consisted primarily of decreased bodyweight and bodyweight gain, liver toxicity such as increased liver weight, hepatocellular hypertrophy with associated changes in clinical chemistry. The LOEL or NOEL established in chronic studies for the different species were: rats (LOEL = 5.5/6.9 mg/kg bw/d, M/F, 104-week), mice (NOEL = 7.8/9.9 mg/kg bw/d, M/F, 80-week study) and dogs (NOEL = 25 mg/kg bw/d, 52-week study).

Mutagenicity/genotoxicity

Isopyrazam was neither mutagenic nor genotoxic in an array of studies including Ames test, cytogenetic assay, chromosomal aberration test and mouse lymphoma mutation assay *in vitro*, and UDS assay and micronucleus test *in vivo*. There was no evidence of a mutagenic/genotoxic potential of mandestrobin or its primary metabolites *in vitro* with and without metabolic activation.

Carcinogenicity

No evidence of oncogenic potential was observed in mice treated with diets containing isopyrazam concentrations up to 3500 ppm (432.6/553.6 mg/kg bw/d, M/F). Isopyrazam is considered to be carcinogenic in rats at a dose of 3000 ppm (173.5/232.8 mg/kg bw/d, M/F), based on the treatment related increase in uterine adenocarcinomas, thyroid follicular cell adenomas in males and hepatocellular adenomas in females (Milburn GM, 2008). The NOEL for carcinogenicity was 500 ppm (27.6/34.9 mg/kg bw/d, M/F) in this study.

Multiple mechanisms of action (MOA) studies were submitted by the applicant postulating mechanism by which isopyrazam induced liver tumours. The available data was analysed using IPCS framework and it was established that isopyrazam-induced rat liver tumours occurs via a MOA that is similar to phenobarbital which is known to be non-genotoxic, a CAR (constitutive androstane receptor)

activator, inducer of liver CYP2B isoforms and induce hepatocellular tumours in rodents but is not a human carcinogen.

The key factors in the weight of evidence evaluation for the carcinogenicity of isopyrazam are: (a) there were no carcinogenic findings in mice in a study where the top dose produced a highly significant decrease in body weight gain (up to 40% in males and up to 20% in females); (b) treatment-related increases in tumour incidence (liver and uterus) were only observed in one sex, one species and confined to a significantly toxic dose level i.e. greater than the MTD (defined as a greater than 10% reduction in body weight gain); (c) isopyrazam was shown not to be oestrogenic in the rat thus excluding the most obvious potential mode of action for uterine tumours; and (d) clear NOELs have been established for liver and uterine tumours indicating that these are a high-dose threshold-based phenomenon.

Reproduction and developmental toxicity

Isopyrazam was not a reproductive or developmental toxicant. The NOEL for reproductive or fertility parameters was 3000 ppm (217.4 mg/kg bw/d) in a two generation rat study.

Neurotoxicity and immunotoxicity

No neurotoxic effects were observed in the acute (single dose) and sub-chronic (90-days) studies in rats. No immunotoxicity findings were observed up to a dose of 5000 ppm (127 mg/kg bw/d) in a 28-day dietary Crl:CD1 female mouse study.

Observation in humans

No information was provided.

Public exposure

No information was provided.

International regulations

Isopyrazam is conditionally approved in the European Union. The United States Environmental Protection Agency (US EPA) has established tolerances for residues of isopyrazam in or on apples and peanuts for which there are no accompanying United States registrations. Isopyrazam is a fungicide not currently registered for use in Canada, however a maximum residue limit (MRL) has been proposed by the Health Canada's Pest Management Regulatory Agency (PMRA) for isopyrazam on bananas to permit the import and sale of foods containing such residues.

Current scheduling status

Isopyrazam is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the Committee has advised the substance meets Schedule 6 criteria, on the basis of acute oral toxicity and potential developmental toxicity being consistent with Schedule 6 factors.

In relation to different isomer mixtures used in testing, the Committee advised that the isomer ratio has an impact on the acute toxicity of isopyrazam but appears to have little influence on repeat-dose effects. The available studies were considered adequate to characterise the toxicity potential of the substance.

In relation to the mode of action for the carcinogenic effects in rats, the Committee advised that the proposed mode of action had not been conclusively demonstrated. However, isopyrazam was not an *in vivo* genotoxicant, and NOELs were identified for tumour findings which were only seen at the top dose levels which exceeded the maximum tolerated dose. The Committee noted the observed tumours in rats were associated with high doses and are not a relevant consideration for scheduling.

The committee advised that a new Schedule 6 entry be created for Isopyrazam as follows:

Schedule 6 - New Entry

ISOPYRAZAM.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: c) Acute oral toxicity and concern for potential developmental 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[14];
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that a new entry for isopyrazam be created in Schedule 6. The delegate notes that this advice is primarily based on the acute toxicity profile, including potential skin sensitisation, being consistent with SPF scheduling criteria for listing in Schedule 6. Also noted are some concerns about the developmental eye defects (microphthalmia) seen in some rabbit studies, although not consistently found in other studies.

The proposed implementation date is **1 October 2016**. An early implementation for this scheduling proposal will facilitate registration of the product by the APVMA.

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

Schedule 6 - New Entry

ISOPYRAZAM

Public submissions on the interim decision

No submissions were received.

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

Delegate's final decision

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

The implementation date is 1 October 2016.

1.15 4,5-Dichloro-2-N-Octyl-3(2H)-Isothiazolone

Referred Delegate's scheduling proposal

- To amend the current 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone Schedule 6 entry to exclude water-based, acrylic or silicone paints, jointing compounds and sealants containing 0.1% or less of 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone. This is a matter that was first considered at the March 2015 ACCS meeting. It is being reconsidered after submission of additional data.

Applicant's application and scheduling proposal

In July 2014, the delegate received the following application to be considered for rescheduling:

- A proposal to amend the current 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone Schedule 6 entry to exclude paints, jointing compounds and sealants containing 0.12% per cent or less of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone from scheduling.

The delegate's interim decision on this proposal was published on the TGA website on 3 June 2015. Following the June 2015 public consultation on the Delegate's interim decision, the applicant provided additional toxicology studies to be considered by the Delegate and/or the committee and a revised proposal for the chemical, limiting the proposed exception to water based/acrylic/silicone paints, jointing compounds and sealants containing 0.1% or less of the chemical.

The applicant's reasons for the request are:

> The applicant proposes that the current entry in Schedule 6 for 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone be amended to exclude water-based, acrylic or silicone paints, jointing compounds and sealants containing 0.1% per cent or less of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone from scheduling and consequently excluding products containing this chemical at a concentration of <0.1% from mandatory packaging and labelling requirements for Schedule 6 chemicals.

Substance summary

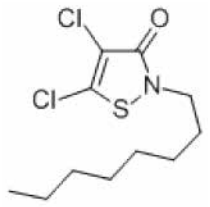

Figure 12: Structure of 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone.

Sensitisation

The relevant sensitisation data for 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone are listed in the table below:

Study	Vehicle	4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone Concentration ppm (%)	Outcome	Test type
O'Hara and Anderson 2002a Reference 3	Paint	300 (0.03) 500 (0.05) 800 (0.08)	Sensitiser Sensitiser Sensitiser	Buehler (Guinea Pigs)
O'Hara and Anderson 2002b Reference 4	Paint	1150 (.12)	Sensitiser	Buehler (Guinea Pigs)
Sanders 2007 Reference 5	Paint	300 (0.03) 600 (0.06) 900 (0.09) 1120 (0.11)	Non sensitiser Non sensitiser Non sensitiser Sensitiser	LLNA (mouse)
	Acetone	300 (0.03) 600 (0.06) 900 (0.09) 1120 (0.11)	Sensitiser Sensitiser Sensitiser Sensitiser	
McMillan 2002 Reference 7	Paint	95 (0.0095) 478 (0.048) 718 (0.072) 947 (0.095) 1094 (0.11)	Non sensitiser Non sensitiser Non sensitiser Non sensitiser Non sensitiser	LLNA (mouse)
	Acetone	95 (0.0095) 478 (0.048) 718 (0.072) 947 (0.095) 1094 (0.11)	Sensitiser Sensitiser Sensitiser Sensitiser Sensitiser	
Sanders 2009 Reference 8	Paint	600 (0.06) 900 (0.09) 1200 (0.12)	Non sensitiser Non sensitiser Sensitiser	LLNA (mouse)

	Acetone/olive oil (4:1)	1200 (0.12)	Sensitiser	
	Acetone	1200 (0.12)	Sensitiser	
Hall 2012 Reference 9	Water based paint	1200 (0.12)	Non sensitiser	Buehler (Guinea Pigs)
	Silicone based paint	1200 (0.12)	Non sensitiser	
	Acetone	800 (0.08)	Sensitiser	

Observation in humans

No information was provided.

Public exposure

No information was provided.

International regulations

As discussed in the previous OCS advice to the delegate, the European Commission (EC) assessment report for 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone as a biocide ingredient in wood preservatives found the chemical to be a skin sensitiser at 0.01% (100 ppm; 4.4 g a.i./cm^2) based on the study considered in March 2015, and recommended that a lower specific concentration limit (lower than the default cut off for skin sensitisers of 1%) should be considered even for classification, labelling and packaging (CLP) for this chemical based on the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (ECHA, 2009). A classification as an extreme sensitizer with a specific concentration of 0.001% was recommended.

The classification, labelling and packaging (CLP) for the chemical based on the Guidance to Regulation (EC) No 1272/2008 applies for occupational use when risk management control measures are expected to be in place at work sites. The extension to use of the products containing the chemical by non-professional painters and possibly the general public would warrant more stringent measures.

Current scheduling status

4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is currently listed in Schedule 6.

Scheduling history

In February 1995, the NDPSC, considered toxicological data for 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone. No metabolic, sub-chronic or chronic animal data was provided. In a 28-day repeat dose study, gastrointestinal irritation was the major toxic effect. Developmental and genotoxicity studies did not show evidence of teratogenicity or genotoxicity. The committee considered that based on its skin and eye corrosion and skin sensitisation potential, it was appropriate to include 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone in Schedule 6.

In June 2008, the NDPSC noted that the toxicology data provided in support of past considerations were very old and that no new data were submitted with the current submission and agreed to defer consideration in order to seek further advice regarding these studies. They agreed however that it was appropriate to proceed with consideration of the applicant's request and decided to broaden the current Schedule 6 exemption of ≤1% in paint by also including ≤1% in jointing compounds and sealants.

In July 2014, the delegate received the following application to be considered for rescheduling:

- A proposal to amend the 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone current Schedule 6 entry to exclude paints, jointing compounds and sealants containing 0.12% or less of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone from scheduling.

The applicant's reasons for the request were:

- 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone is a film biocide used in paints, jointing compounds and sealants to provide fungicide protection to stop the growth of mould. Given the nature of these products, their packaging and use, oral ingestion of any significant amounts of the formulated product is unlikely. The proposed exemption cut-off concentration of 0.12% is low, exposure would be accidental and based on the pharmacology of the substance, any associated absorption would be minimal with clearance within 2 days and no evidence of accumulation once absorbed.
- The proposal aims to provide 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone with an exemption from scheduling in the same manner that specified concentrations of carbendazim and octhilinone are exempt. Carbendazim and octhilinone have been extensively considered by scheduling committees over a 40 year period. Hence, there is considerable precedent related to this proposal and the relevant matters under 52E(1): the risks and benefits, potential hazards, extent and patterns of use and dosage and formulation have previously been considered for carbendazim and octhilinone resulting in exemption cut-offs for both substances.
- On the basis of the toxicological data presented in this submission, 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is a safer, suitable alternative film biocide to carbendazim (excluded from Schedule 7 at 0.1% or less) and is an isothiazolinone structurally-related to the film biocide octhilinone (excluded from Schedule 6 at 1% or less); however, without an exemption from Schedule 6, 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is not regulated in the same manner as carbendazim and octhilinone.

In June 2015 the interim decision of the Delegate was published noting that the current Schedule 6 entry was appropriate. In response to the Delegate's interim decision, the applicant provided additional toxicology studies to be considered by the Delegate and/or the committee and a revised proposal for the chemical, limiting the exception to water based/acrylic/silicone paints, jointing compounds and sealants containing 0.1% or less of the chemical.

Pre-meeting public submissions

One public submission was received. The submission supports the proposed amendments and notes skin contact for paints is incidental during use, and do not remain on the skin thus sensitization risks are minimal.

The public submission is available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the committee has advised there is insufficient evidence to support the proposed cut off for exemption. New animal studies indicate that skin sensitisation can occur at levels either around or below the cut off proposed by the applicant. Skin exposure during the use of the paint is highly likely in the domestic setting with a significant risk of skin sensitisation necessitating label warnings and the substance retention in Schedule 6.

On the weight that should be given to the applicant's contention that the substance is substantially retained in the paint matrix and is therefore not available for absorption into the skin, the Committee advised this was most relevant for applied and dried paint. However, it was noted studies provided indicate up to 20% of the substance was available for absorption and, given the very low concentrations that elicited a response in the animal tests, the reduced absorption does not eliminate the risk of skin sensitisation.

On the Delegate's question about LLNA and Buehler tests, the Committee advised that positive test results from one method should not automatically be dismissed in favour of negative findings using the other method. The Committee noted no testing results were provided for product types other than paint, such as jointing compounds and sealants.

The committee advised that the current Schedule 6 entry for 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone remains appropriate.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: b) Incidental dermal exposure is likely with inclusion of the substance as a biocide in paints, jointing compounds and sealants, particularly when these products are used by the general public.; c) Animal studies suggest skin sensitisation is possible at very low concentrations and therefore the substance, at all concentrations, continues to meet the criteria for 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[15];
- Other relevant information.

Delegate's interim decision

The delegate notes the advice from the ACCS based on evaluation of additional information submitted by the applicant since this matter was considered at the March 2015 ACCS meeting. The delegate agrees that the new studies suggest a reduction in sensitisation potential when 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is incorporated in a paint matrix, but that they do not resolve the question of where an appropriate exemption cut-off could be applied to such products. Findings that sensitisation reactions have been demonstrated at and below the proposed cut-off concentrations support the ACCS advice that current scheduling remains appropriate, and that the sensitisation warning statements and POISON signal heading on such products provide appropriate advice to product users.

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

Public submissions on the interim decision

One submission was received that disagreed with the assessment made of the sensitisation potential for 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone when incorporated into a water-based paint matrix and requested further consideration of an exemption for concentrations up to 1000 ppm, with additional data provided.

Delegate's final decision

The delegate notes the issues raised in the late submission relating to the proposed exemption from the current Schedule 6 entry for water-based paints and sealants containing

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

4,5-dichloro-2-N-octyl-3(2H)-isothiazolone at up to 1000 ppm. The delegate has defer making a final decision for this substance pending further consideration of the late submission.

1.16 Methyldibromo glutaronitrile

Referred Delegate's scheduling proposal

- To resolve an apparent ambiguity between the Schedule 6 and Schedule 10 entries relating to duplication of the exception clause "except in preparations intended to be in contact with the skin, including cosmetic use".

Applicant's application and scheduling proposal

On 30 November 2015 the chemicals scheduling Delegate identified possible ambiguity in the current SUSMP entries for the chemical. The proposal is to amend the Schedule 6 entry to remove the exception clause "except in preparations intended to be in contact with the skin, including cosmetic use".

Substance summary

Please refer to the NICNAS Chemical assessment report for methyldibromo glutaronitrile which is available from the NICNAS website.

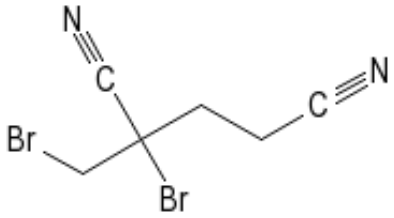

Figure 13. Structure of methyldibromo glutaronitrile

Public exposure

No information provided.

International regulations

No information provided.

Current scheduling status

Methyldibromo glutaronitrile is currently listed in Schedules 6 and 10 and Appendix F.

Schedule 6

METHYLDIBROMO GLUTARONITRILE **except** in preparations intended to be in contact with the skin, including cosmetic use.

Schedule 10

METHYLDIBROMO GLUTARONITRILE in preparations intended to be in contact with the skin, including cosmetic use **except** when in Schedule 6.

Appendix F, Part 3

Warning statement 28

Safety directions 1, 4, 7

Scheduling history

Methyldibromo glutaronitrile (MDBG) was first considered for scheduling in June 2008. Due to an administrative error the substance was reconsidered at the October 2008 meeting.

The Committee decided: to include MDBG in Appendix C when in preparations intended to be in contact with the skin, including cosmetic use; and in Schedule 6 **except** when in preparations intended to be in contact with the skin, including cosmetic use. Appendix F warning statement 28 and Safety directions 1, 4 and 7 were also agreed.

The current wording of the Schedule 10/Appendix C entry was published in the first version of the Standard in 2015 https://www.legislation.gov.au/Details/F2015L00128.

Pre-meeting public submissions

Two public submissions were received. The first submission did not support the proposed amendments. They noted that MDBG is entered in the ARTG ingredient list and is allowed in therapeutic goods as an excipient in OTC medicines. They requested that the ACCS considers exemptions (from either Schedule 6 or Schedule 10, as appropriate) for the use of the substance as an excipient in therapeutic goods, with a suitable cut-off concentration if appropriate. The second submission supports clarification of the current Schedule entries and included proposed wording for an amended Schedule 6 entry.

The public submissions are available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the Committee advised that the current schedule entries for MDBG were ambiguous. They recommended that the entries could be improved by simplifying the cross reference between the entries as follows; for the schedule 6 entry, replacing the exception clause with "except when in Schedule 10", and for the Schedule 10 entry, referring to the use that is subject to prohibition and deletion of reference to the Schedule 6 entry.

The Committee recommended the following amendments to the Poisons Standard:

Schedule 6 - Amend Entry

METHYLDIBROMO GLUTARONITRILE **except** when in Schedule 10.

Schedule 10 - Amend Entry

METHYLDIBROMO GLUTARONITRILE in preparations intended to be in contact with the skin, including cosmetic use.

The Committee recommended an early implementation date of 1 October 2016.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: f) amendments clarify which uses are subject to prohibition in Schedule 10.

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[16];
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, ACCS advice to amend the Schedule 6 and 10 entries for methyldibromo glutaronitrile, since they appeared to contain mutually exclusive exemption clauses. The purpose of the Schedule 10 entries was to prevent the availability of products that would be directly applied to human skin. Retaining the existing Schedule 6 entry would be consistent with SPF criteria for such a listing and would ensure that labelling and supply restrictions for other types of products are retained.

The delegate notes the industry submission that seeks an exemption from the entries where the substance may be used in therapeutic goods. The chemicals scheduling delegate has therefore referred the matter to the medicines scheduling delegate for further consideration.

The proposed implementation date is **1 October 2016**. This is a clarification of existing schedule entries, so it should be implemented in the earliest revision of the Poisons Standard.

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 6 - Amend Entry

METHYLDIBROMO GLUTARONITRILE **except** when in Schedule 10.

Schedule 10 - Amend Entry

METHYLDIBROMO GLUTARONITRILE in preparations intended to be in contact with the skin, including cosmetic use.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

1.17 Potassium Hydroxide and Sodium Hydroxide

Referred Delegate's scheduling proposal

- Amend the existing Schedule 6 or 10 entries to address possible ambiguities in the duplication of the exception clause c) that relates to liquid or semi-solid food additive preparations, the pH of which is more than 11.5, for domestic use.

Applicant's application and scheduling proposal

On 30 November 2015 the Chemicals Scheduling Delegate identified ambiguity in the current entries for sodium and potassium hydroxide in relation to the use in food additive preparations. The proposal is to delete the exception clause c) in the Schedule 6 entries for potassium hydroxide and sodium hydroxide.

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

The reason for the request is:

> The Schedule 10 entry prohibits use as a food additive except where in Schedule 6; however the Schedule 6 entry excludes the use as a food additive ingredient.

Substance summary

Please refer to the NICNAS assessment reports for sodium hydroxide and potassium hydroxide available on the NICNAS website.

Public exposure

No information was provided.

International regulations

No information was provided.

Current scheduling status

Sodium hydroxide and potassium hydroxide are currently listed in Schedules 5, 6 and 10 of the SUSMP. They are also included in Appendix E and F.

Schedule 5

POTASSIUM HYDROXIDE (excluding its salts and derivatives) in preparations containing 5 per cent or less of potassium hydroxide being:

a) solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5; or

b) liquid or semi-solid preparations, the pH of which is more than 11.5 except in food additive preparations for domestic use.

SODIUM HYDROXIDE (excluding its salts and derivatives) in preparations containing 5 per cent or less of sodium hydroxide being:

a) solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5; or

b) liquid or semi-solid preparations, the pH of which is more than 11.5 except in food additive preparations for domestic use.

Schedule 6

POTASSIUM HYDROXIDE (excluding its salts and derivatives) **except**:

a) when included in Schedule 5;

b) in preparations containing 5 per cent or less of potassium hydroxide being:

   i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

   ii) liquid or semi-solid preparations, the pH of which is 11.5 or less; or

c) in liquid or semi-solid food additive preparations, the pH of which is more than 11.5, for domestic use.

SODIUM HYDROXIDE (excluding its salts and derivatives) **except**:

a) when included in Schedule 5;

b) in preparations containing 5 per cent or less of sodium hydroxide being:

   i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

ii) liquid or semi-solid preparations, the pH of which is 11.5 or less; or

c) in liquid or semi-solid food additive preparations, the pH of which is more than 11.5, for domestic use.

Schedule 10

POTASSIUM HYDROXIDE (excluding its salts and derivatives), in liquid or semi-solid food additive preparations, for domestic use, the pH of which is more than 11.5.

SODIUM HYDROXIDE (excluding its salts and derivatives), in liquid or semi-solid food additive preparations, for domestic use, the pH of which is more than 11.5.

Scheduling history

Potassium and sodium hydroxides were first considered for scheduling at the May 1956 and January 1955 meetings, respectively. They have since been considered a number of times, most recently at the February 2010 meeting. At this meeting the Committee discussed the inherent properties of lye water and its poisoning risk – particularly consequences of accidental ingestion by children. It was noted that the lye water accidental poisoning issue was considered at previous meetings and at that time the Committee had decided that the risks from lye water with a pH of more than 11.5 were adequately addressed through a CRC requirement (along with public education and labelling). Several Members asserted that the information now before the Committee was sufficient to establish that this existing level of control had not been sufficient, noting lye water accidental ingestions and injuries had continued to occur since the mandating of CRCs.

Members generally agreed that, for lye water preparations with a pH of more than 11.5, the extremely alkaline nature, even in small amounts, could cause life threatening caustic injuries. A Member noted, however, that the risk of ingestion was most significant with regard to use in the domestic setting. The Member argued that there appeared to be scope for continuing to allow non-domestic access (such as restaurants or industrial food processing) to high strength lye water products. Another Member noted that there appeared to be alternative preparations available with pH of 11.5 or less which should be sufficient for domestic use. The Committee therefore agreed to restrict the domestic availability of lye water by capturing domestic food additive preparations, with pH of more than 11.5, through specific entries to this effect for alkaline salts, sodium hydroxide and potassium hydroxide in Appendix C.

Pre-meeting public submissions

One public submission was received. That submission supported the proposed amendments to remove ambiguity in those entries. The submission provided suggested wording for the revised entry.

The public submissions are available at the TGA website.

Summary of ACCS advice to the delegate

In response to the Delegate's request, the Committee have advised that the KOH and NaOH entries are ambiguous, and that amendment to the Schedule 6 entries would provide greater clarity.

The Committee advised that, with the availability of an electronic version of the SUSMP it was now easy for users to do a search of the document to find all relevant entries and inserting a dagger was now unnecessary.

The Committee recommended that the current Schedule 6 entries for potassium hydroxide and sodium hydroxide be amended as follows:

Schedule 6 - Amend Entry

POTASSIUM HYDROXIDE (excluding its salts and derivatives) **except**:

a) when included in Schedule 5 or 10; or

b) in preparations containing 5 per cent or less of potassium hydroxide being:

i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

ii) liquid or semi-solid preparations, the pH of which is 11.5 or less; or

SODIUM HYDROXIDE (excluding its salts and derivatives) **except**:

a) when included in Schedule 5 or 10; or

b) in preparations containing 5 per cent or less of sodium hydroxide being:

i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

ii) liquid or semi-solid preparations, the pH of which is 11.5 or less.

The Committee recommended an early implementation date (1 October 2016).

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: f) Amendment further clarifies existing entries.

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[17];
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, ACCS advice to amend the Schedule 6 entries for sodium and potassium hydroxides, since they appeared to contain an exemption clause that contradicts the purpose of the Schedule 10 entry. The purpose of the Schedule 10 entries was to prevent the availability of such strongly alkaline solutions for use as food additives in the domestic market. The proposed cross-reference in the Schedule 6 entries to the entries in both Schedules 5 and 10 should clarify the intent of these controls. The delegate notes that the proposed amendments are supported by the submission from industry.

The proposed implementation date is **1 October 2016**. This is a clarification of existing schedule entries, so it should be implemented in the earliest revision of the Poisons Standard.

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

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

Schedule 6 - Amend Entry

POTASSIUM HYDROXIDE (excluding its salts and derivatives) **except**:

a) when included in Schedule 5 or 10; or

b) in preparations containing 5 per cent or less of potassium hydroxide being:

   i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

   ii) liquid or semi-solid preparations, the pH of which is 11.5 or less; or

SODIUM HYDROXIDE (excluding its salts and derivatives) **except**:

a) when included in Schedule 5 or 10; or

b) in preparations containing 5 per cent or less of sodium hydroxide being:

   i) solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

   ii) liquid or semi-solid preparations, the pH of which is 11.5 or less.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

The implementation date is 1 October 2016.

2. Scheduling proposals referred to the March 2016 meeting of the Advisory Committee on Medicines Scheduling (ACMS#17)

Summary of delegate's final decisions

Substance	Final decision
Benzodiazepine derivatives	**Schedule 9 - New Entries** DICYCLAZEPAM. PYRAZOLAM. CLONAZOLAM. DESCHLOROETIZOLAM. FLUBROMAZEPAM. NIFOXIPAM. MECLONAZEPAM. Implementation date: 1 October 2016.
Ketoprofen	Current scheduling remains appropriate.
Naproxen	Current scheduling remains appropriate.
Paracetamol	**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 primary pack containing no more than 12 dosage units per pack; or b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

Substance	Final decision
	d) in other preparations **except:** i) when included in Schedule 3 or 4; or 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 RASML. (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 that contains not more than 20 tablets or capsules. (C) compliant with the requirements of the RASML. (D) not labelled for the treatment of children 6 years of age or less. (E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin. **SCHEDULE 3 - Current Entry** PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2. **SCHEDULE 4 - Amend entry** PARACETAMOL: a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in the Schedules;

Substance	Final decision
	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; f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2; g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2; h) for injection. Current Appendix F entries for paracetamol remain appropriate. Implementation date: 1 October 2016.
Loratadine	**SCHEDULE 2 - Amend Entry** LORATADINE in preparations for oral use except in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: a) in a primary pack containing 10 dosage units or less; and b) labelled with a recommended daily dose not exceeding 10 mg of loratadine. **SCHEDULE 4 -Amend Entry** LORATADINE except: a) when included in Schedule 2; or b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: i) in a primary pack containing 10 dosage units or less; and ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine. Implementation date: 1 October 2016.

2.1 Benzodiazepine derivatives

Referred Delegate's scheduling proposal

To delete the Schedule 4 entry of BENZODIAZEPINE DERIVATIVES and create a new Schedule 9 or Schedule 8 entry for BENZODIAZEPINE DERIVATIVES with an exception for benzodiazepines listed separately in the Schedules.

Applicant's application and scheduling proposal

Delegate-initiated application. The reason for the request was:

- At the ACMS meeting November 2015, the Committee advised that the Schedule 4 entry of BENZODIAZEPINE DERIVATIVES be deleted and create a new entry with the same wording in Schedule 9.

Substance summary

Benzodiazepines are the major group of drugs used as anxiolytics and hypnotics, with some also used for their muscle relaxant and anticonvulsant properties. Benzodiazepines may be helpful in the short-term management of anxiety and sleep disturbances, but they must be used with caution because of the risk of dependence and abuse, even when used at therapeutic doses for short periods. Some commonly used benzodiazepines include diazepam, oxazepam, nitrazepam and temazepam.

Current scheduling status

A class entry for Benzodiazepine derivatives is currently listed in Schedule 4, except when separately specified in the Schedules. The majority of individually listed benzodiazepines are in Schedule 4.

Scheduling history

Benzodiazepines were listed in Schedule 4 as a class entry in the Poisons Standard ensuring new benzodiazepine derivatives, including those prepared by simple manipulation of drug molecules, would be captured by the existing Schedule entry, in accordance with the United Nations Convention on Psychotropic Substances 1971 (the Convention).

In May 1986 in response to a request from the Western Australian Health Department, the Committee agreed to include 10 separate benzodiazepine substances in Schedule 4 and amend the benzodiazepine class entry to exclude those that were separately specified.

In February 1987, the individual benzodiazepine substances were listed in Appendix K as drugs required to be labelled with warning statements.

In February 1996, the National Drugs and Poisons Schedule Committee (NDPSC) considered a report of an overdose resulting in death and the New South Wales State Coroner concerns regarding the appropriateness of the current benzodiazepines scheduling. The Committee considered the new information, and concluded that rescheduling of the drugs would not have prevented the overdose, noting that the States and Territories have procedures in place to deal with such matters and that the appropriate prescription and dispensing of Schedule 4 drugs to be the professional responsibility of medical practitioners and pharmacists. The Committee considered that benzodiazepines were appropriately scheduled in Schedule 4 and that strategies other than those available via the scheduling mechanism were more appropriate.

In November of 1997, the benzodiazepine substance flunitrazepam was rescheduled from Schedule 4 to Schedule 8 due to public health concerns. The NDPSC agreed that, while from a scientific standpoint flunitrazepam is no different from other substances in the benzodiazepine class, the health concerns related to the use and accessibility of flunitrazepam lead to its inclusion in Schedule 8.

In August of 1998, a class review of benzodiazepines based on the up-scheduling of flunitrazepam was conducted by the committee. The NDPSC recognised that benzodiazepines were useful therapeutic

products and generally there are no suitable substitutes for their legitimate therapeutic uses. The Committee also noted that rescheduling would impose additional difficulties and costs for manufacturers, pharmacists, patients and the PBS system. A majority of the public submissions received advocated for the retention of benzodiazepines in Schedule 4, resulting in no change to the scheduling. The appropriateness of the scheduling was again reaffirmed in 1999.

Alprazolam was scheduled in November 1981, and was added to Appendix K in November 1987 as it was included in a list of substances of concern by the Australian Federal Police. In October 2007, the Department of Health in Tasmania introduced monthly reporting requirements of Alprazolam due to concerns of misuse. Rescheduling Alprazolam as a Schedule 8 substance was considered in June 2010. However, there was insufficient evidence to support a Schedule 8 restriction for alprazolam, and advised that the Schedule 4 entry remained appropriate.

In November 1971, temazepam is individually specified in Schedule 4, with appendix K entry added in February 1987. At the February and June 2004 meetings, the NDPSC considered a proposal to reschedule temazepam soft gel capsules to Schedule 8 due to illicit drug abuse market. Following the deferral from the February meeting, the sponsor of the product voluntarily withdrew the soft gel capsule products from the ARTG, with temazepam remaining in Schedule 4.

The following benzodiazepines were included in Schedule 4 by individual specification between 1965 and 1998 without an Appendix K entry: Bromazepam, Chlordiazepoxide, Clonazepam, Clorazepate, Clobazam, Diazepam, Flurazepam, Ketazolam, Loprazolam, Lorazepam, Lormetazepam, Medazepam, Midazolam, Nitrazepam, Oxazepam, Prazepam, Quazepam and Triazolam.

In 2013, the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8. The Committee recommended: (1) that alprazolam be rescheduled from Schedule 4 to Schedule 8; (2) that the scheduling of the remaining benzodiazepines remained appropriate; and (3) that benzodiazepines be included in Appendix D, paragraph 5.

Pre-meeting public submissions

No submissions were received.

Summary of ACMS advice to the delegate

The Committee advised that the:

- following substances, not previously scheduled, be separately specified in Schedule 9: dicyclazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazepam, nifoxipam and meclonazepam.
- current scheduling of benzodiazepine derivative (Class entry) otherwise 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 advice comprised the following:
  - Potential for abuse is high, with possible future compounds being designed to increase abuse potential.
  - Benefit may include potential for new drug classes that have not been developed for different therapeutic use.

- Some substances captured by the term "Benzodiazepine derivatives" are marketed overseas as legitimate medicines. This term should remain in the same schedule as the majority of individually listed benzodiazepines, namely Schedule 4.
- The term "Benzodiazepine derivatives" captures both substances with legitimate medical uses and substances primarily used as drugs of abuse. Although longer term use of benzodiazepines results in physical dependency the potential for abuse of the class overall would fit the criteria for a Schedule 4 substance.
- New entries in Schedule 9 for dicyclazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazepam, nifoxipam and meclonazepam as they currently have no known therapeutic use in Australia and are contained in no registered products, but are available overseas.

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[18];

· Other relevant information.

Delegate's interim decision

The delegate's interim decision is that:

· dicyclazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazepam, nifoxipam and meclonazepam, not previously scheduled, be separately specified in Schedule 9; and

· the current scheduling of other benzodiazepines remains appropriate.

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: 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; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the decision comprised the following:

· Potential for abuse is high, with possible future compounds being designed to increase abuse potential.

· Benefit may include potential for new drug classes that have not been developed for different therapeutic use.

· Some substances captured by the term "Benzodiazepine derivatives" are marketed overseas as legitimate medicines. This term should remain in the same schedule as the majority of individually listed benzodiazepines, namely Schedule 4.

· The term "Benzodiazepine derivatives" captures both substances with legitimate medical uses and substances primarily used as drugs of abuse. Although longer term use of benzodiazepines results

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

in physical dependency the potential for abuse of the class overall would fit the criteria for a Schedule 4 substance.

- New entries in Schedule 9 for dicyclazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazepam, nifoxipam and meclonazepam as they currently have no known therapeutic use in Australia and are contained in no registered products, but are available overseas.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

2.2 Ketoprofen

Delegate's scheduling proposal

Proposal to amend the scheduling of ketoprofen to include divided preparations for oral use containing 200 mg or less of ketoprofen per dosage unit in Schedule 3.

Applicant's application and scheduling proposal

To amend the scheduling of ketoprofen to include divided preparations for oral use containing 200 mg or less of ketoprofen per dosage unit in Schedule 3.

The reasons for the request are:

- The doses that are able to alleviate or cure tenosynovitis are larger than those currently available through Schedule 3; and
- Ketoprofen is able to be ordered through UK, USA or Spanish websites at 50 mg or 100 mg of ketoprofen per dosage unit.

Substance summary

Ketoprofen, a propionic acid derivative, is non-steroidal anti-inflammatory drug (NSAID) and has been marketed for the treatment of rheumatoid arthritis and osteoarthritis in various forms (standard release capsules, sustained release capsules, suppositories and topical gels).

Current scheduling status

KETOPROFEN is currently listed in Schedules 3 and 4.

Scheduling history

Ketoprofen has been available in Australia since 1981 in orally administered dose forms.

In 1999, the National Drugs and Poisons Schedule Committee decided to harmonise with New Zealand in regard to oral and dermal preparations of ketoprofen – creating the Schedule 3 entry for 25 mg or less of ketoprofen per dosage unit in a pack containing 30 or less dosage units.

Pre-meeting public submissions

Two submissions were received. Both submissions opposed the proposal due to increased risks of gastrointestinal and cardiovascular adverse effects compared to other NSAIDs available over the counter (i.e. ibuprofen, diclofenac and naproxen).

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The Committee advised that the current scheduling of ketoprofen 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; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice comprised the following:

- Risks include increased gastrointestinal and cardiovascular adverse effects compared to other NSAIDs available over the counter (i.e. ibuprofen, diclofenac and naproxen).
- Ketoprofen is not recommended for use while breastfeeding and there is increased risk of adverse effects in the elderly.
- Ketoprofen is registered for use in the treatment of rheumatoid arthritis and osteoarthritis.
- Common toxicity issues related to the substance include: nausea, dyspepsia, GI ulceration/bleeding, raised liver enzymes, diarrhoea, headache, dizziness, salt retention and hypertension.
- The substance is available in 200 mg controlled release oral capsules and 100 mg suppositories.

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[19];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the current scheduling of ketoprofen 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; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the decision comprised the following:

- Risks include increased gastrointestinal and cardiovascular adverse effects compared to other NSAIDs available over the counter (i.e. ibuprofen, diclofenac and naproxen).
- Ketoprofen is not recommended for use while breastfeeding and there is increased risk of adverse effects in the elderly.
- Ketoprofen is registered for use in the treatment of rheumatoid arthritis and osteoarthritis.
- Common toxicity issues related to the substance include: nausea, dyspepsia, GI ulceration/bleeding, raised liver enzymes, diarrhoea, headache, dizziness, salt retention and hypertension.

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

- The substance is available in 200 mg controlled release oral capsules and 100 mg suppositories.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

2.3 Naproxen

Referred Delegate's scheduling proposal

Proposal to amend the Schedule 2 naproxen entry to exclude naproxen (i.e. make it available for sale outside pharmacy) when containing 200 mg or less of naproxen per dosage unit in packs of 12 or less dosage units when not labelled for the treatment of children under 12 years of age.

Applicant's application and scheduling proposal

To amend Part 4, Schedule 2 naproxen entry to exclude naproxen in a dosage form of 200 mg or less of naproxen per dosage unit in packs of 12 or less dosage units when not labelled for the treatment of children under 12 years of age.

The Applicant's reasons for the request are:

- The proposal to amend the current Schedule 2 naproxen entry to exclude naproxen 200 mg solid oral dosage forms in a limited few days' supply. This would be packaged and labelled with restrictions and conditions that are consistent, if not more conservative, than the current unscheduled OTC ibuprofen preparations.
- Local and global post-marketing experiences, overseas regulatory status in comparable markets (such as Canada and the USA), as well as various published safety data, help support the approval for an open-sale supply of naproxen in Australia. This indicates no greater health risk to the public than the current Schedule 2 scheduling for naproxen and/or the scheduling exemption for ibuprofen, when compared with the proposed amendment.
- The open-sale of naproxen would provide consumers with a wider access to, and added option for, self-medicate for mild to moderate conditions including body aches, muscle and period pain.

Substance summary

Naproxen is an arylpropionic acid derivative related to the arylacetic acid class of medicines. It has analgesic, anti-inflammatory and antipyretic properties. It is unrelated to salicylates and the corticosteroid hormones. Naproxen therapeutic indications include treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis; symptomatic treatment of primary dysmenorrhoea and relief of acute and/or chronic pain states in which there is an inflammatory component as well as an analgesic in acute migraine attack.

Naproxen is a non-selective non-steroidal anti-inflammatory drug (NSAID) inhibiting both COX-1 and COX-2 and it exhibits a pharmacologic profile similar to other compounds in the NSAID class, such as ibuprofen. Naproxen has been widely used as a prescription and OTC medicine for many years, and its safety profile has been well-characterised.

Current scheduling status

Naproxen is currently listed in Schedules 2, 3 and 4, and in Appendix F. The delegate in November 2015 decided that from 1 June 2016, naproxen will also be in Schedule H.

SCHEDULE 2

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

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 2 or 3.

Appendix F

Poison	Warning Statements
Naproxen	101: Don't use [*this product/name of the product*]: If you have a stomach ulcer. In the last 3 months of pregnancy. [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea*.] If you are allergic to (name of substance) or anti-inflammatory medicines.
	104: Unless a doctor has told you to, don't use [*this product/name of the product*]: For more than a few days at a time. With other medicines containing (name of substance) or other anti-inflammatory medicines. If you have asthma. If you are pregnant. [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea*.]

Scheduling history

Naproxen was first included in Schedule 4 of the Poisons Standard in June 1982.

In February 1983, the Poisons Scheduling Committee (PSC) agreed to reschedule naproxen from Schedule 4 to Schedule 3 when supplied in packs of 12 tablets for the treatment of the symptoms of dysmenorrhea.

In August 1989, a new Schedule 2 entry for naproxen was supported by the Drugs and Poisons Schedule Committee (DPSC) when labelled for the treatment of spasmodic dysmenorrhoea in packs of 12 or less on the grounds that it did not present an apparent public health hazard.

In November 1998, the National Drugs and Poisons Schedule Committee (NDPSC) amended the Schedule 2 entry for naproxen to allow preparations containing 250 mg or less per dosage unit in packs of 20 or less dosage units.

In November 1999, the NDPSC rescheduled the Schedule 3 entry to Schedule 2 on the basis that the safety data was similar to that of other NSAIDs already listed in Schedule 2. An Appendix F warning was linked to the Schedule 2 entry.

In August 2001, the NDPSC considered a proposal to exempt naproxen when in 250 mg or less per dosage unit, in packs of 24 or less dosage units, for the short-term analgesic therapy of dysmenorrhoea. The committee decided that the Schedule 2 entry remained appropriate given concerns around lack of evidence regarding safety and the need to access advice and counselling.

In May 2005, warning statements 101 and 104 were included in Appendix F.

In March 2014 (delegate decision July 2014), the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal to include naproxen in Schedule 2 in a new 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 advised, and the delegate decided, that those modified release naproxen preparations should be included in Schedule 3. The ACMS also advised that the existing Appendix F warnings for naproxen should apply to the new Schedule 3 dosage form for naproxen. This was implemented on 1 October 2014.

In November 2014, the ACMS rejected a proposal to include naproxen (when in Schedule 3, which covers only modified release naproxen) in Appendix H, citing 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.

In November 2015, the ACMS advised, and the delegate agreed, to include naproxen in Appendix H. The implementation date is 1 June 2016.

Pre-meeting public submissions

Three submissions were received. One submission supported the proposal. The main points were:

- Comparable products (ibuprofen, paracetamol and aspirin) are exempt from scheduling when in small packs and has a well-established safety profile.
- Consumer would benefit.

Two submissions opposed the proposal. The main points were:

- ACMS considered a similar proposal in November 2014 (to include naproxen in Appendix H) and concluded the current scheduling is appropriate, due to the gastrointestinal risk being greater than ibuprofen. [Note: naproxen is in Appendix H as of 1 June 2016]
- There would be an increased risk to consumers with cardiovascular complications, particularly elderly consumers.
- Greater emphasis should be placed on communicating to consumers the relevant risk factors and the need to limit dose and duration of treatment.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The Committee advised that the current scheduling of naproxen 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; f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Naproxen carries a higher risk of gastrointestinal toxicity than ibuprofen. The risk of cardiovascular toxicity associated with use of OTC naproxen is likely to be the same as that for OTC ibuprofen.

- Use of medicines for the relief of pain is common. A greater risk of gastrointestinal toxicity associated with the use of naproxen is likely to be significant if the use of naproxen increased as a result of it being available as an unscheduled medicine.
- No consumer experience in Australia for OTC naproxen except for use in period pain.
- There is evidence that administration of naproxen results in an increased incidence of serious upper gastrointestinal toxicity when compared with other NSAIDs.
- The individual dose unit strength of the naproxen in the submission is different from that currently available, creating possible confusion amongst consumers.

Availability of naproxen as an unscheduled medicine is unlikely to provide a greater consumer health benefit when compared with use of ibuprofen as an unscheduled medicine or naproxen as a Schedule 2 medicine. If unscheduled ibuprofen is inadequate for pain relief it is preferable that the consumer access health professional advice regarding the appropriate pain management.

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[20];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the current scheduling of naproxen 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; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the decision comprised the following:

- Naproxen carries a higher risk of gastrointestinal toxicity than ibuprofen. The risk of cardiovascular toxicity associated with use of OTC naproxen is likely to be the same as that for OTC ibuprofen.
- Use of medicines for the relief of pain is common. A greater risk of gastrointestinal toxicity associated with the use of naproxen is likely to be significant if the use of naproxen increased as a result of it being available as an unscheduled medicine.
- No consumer experience in Australia for OTC naproxen except for use in period pain.
- There is evidence that administration of naproxen results in an increased incidence of serious upper gastrointestinal toxicity when compared with other NSAIDs.
- The individual dose unit strength of the naproxen in the submission is different from that currently available, creating possible confusion amongst consumers.

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

Availability of naproxen as an unscheduled medicine is unlikely to provide a greater consumer health benefit when compared with use of ibuprofen as an unscheduled medicine or naproxen as a Schedule 2 medicine. If unscheduled ibuprofen is inadequate for pain relief it is preferable that the consumer access health professional advice regarding the appropriate pain management.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

2.4 Paracetamol

Referred Delegate's scheduling proposal

Proposal to amend the Schedule 2 entry of paracetamol to:

- restrict the pack size requirements to no more than 100 tablets or capsules per pack and no more than 50 wrapped powders or sachets of granules per pack for domestic supply, and
- specifically limit bulk pack sizes of paracetamol for supply only to hospital, nursing homes and pharmacies for dispensing purposes.

Applicant's application and scheduling proposal

OTC Medicines Evaluation (OTCME, Department of Health) application.

To amend the Schedule 2 entry of paracetamol to (a) restrict the pack size requirements to no more than 100 tablets or capsules per pack and no more than 50 wrapped powders or sachets of granules per pack for domestic supply, and (b) specifically limit bulk pack sizes of paracetamol for supply only to hospitals, nursing homes and pharmacies for dispensing purposes.

The reasons for the request are:

- The OTCME has received enquiries regarding proposals to register packs containing more than 100 tablets or capsules per pack of paracetamol for direct sale to consumers. The Poisons Standard currently does not impose a pack size limit for paracetamol as a Schedule 2 medicine.
- The OTCME regards larger pack sizes (more than 100 tablets or capsules per pack) when supplied as Schedule 2 for sale in pharmacies as having an unacceptable risk to safety (due to deliberate self-poisoning).

Substance summary

Paracetamol, also known as acetaminophen, is an analgesic substance used to treat pain and fever. It is typically used for treatment of mild to moderate pain and is often sold in combination with other ingredients in cold medications.

Current scheduling status

Products containing paracetamol in combination with ibuprofen are currently included in Schedules 2, 3 and 4.

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

SCHEDULE 2

PARACETAMOL for therapeutic use**:**

a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack.

b) In other preparations **except:**

i) when included in Schedule 3 or 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 RASML.

(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 that contains not more than 20 tablets or capsules.

(C) compliant with the requirements of the RASML.

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

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

SCHEDULE 3

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

SCHEDULE 4

PARACETAMOL:

a) when combined with aspirin or salicylamide or any derivative of these substances **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.

Appendix F

Poison	Warning Statements
Paracetamol	97: Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor. and/or
	98: Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.
	99: If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.
	100: Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.

Scheduling history

In October 2003, the NDPSC considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter paracetamol for inclusion in Appendix F of the Poisons Standard. The Committee agreed to the inclusion of the MEC proposed new label warning statements for paracetamol in Appendix F the SUSDP and the consequential amendments to the Schedule 2 entry for paracetamol. It was also agreed that the effective date would be 1 May 2005.

In 2006, the NDPSC considered and supported a recommendation from the Medicines Classification Committee (MCC) to harmonise on the requirement for Schedule2 tablets or capsules containing over 500 mg and up to 665 mg of paracetamol to be in slow release form only.

In February 2008, the NDPSC considered and supported a proposal to include paracetamol for injection in Schedule 4.

Pre-meeting public submissions

Four submissions were received all supporting the proposal. The main points were:

- Restrictions in maximum pack size in Schedule 2 be 50 tablets/capsules and no more than 25 wrapped powder or sachets be considered.
- ACMS to consider whether the proposed Schedule 2 amendment is consistent with the lack of controls over the number of paracetamol products that can be purchased outside a pharmacy.
- Efficiency for dispensaries with the prevention of de-blistering individual tablets.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the Schedule 2 (and Schedule 4) entry for paracetamol be amended to:

SCHEDULE 2 – Amend Entry

PARACETAMOL for therapeutic use:

(a) in tablets or capsules enclosed in a primary pack containing *not more than 100 tablets or capsules* **except** 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 containing not more than 20 tablets or capsules;

(iii) compliant with RASML requirements;

(iv) not labelled for the treatment of children 6 years of age or less; and

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

(b) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient' (or words to that effect); or

(c) in individually wrapped powders or sachets of granules enclosed in a primary pack containing *not more than 50 wrapped powders or sachets of granules* **except** in 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 containing not more than 10 such powders or sachets of granules;

(ii) compliant with RASML requirements;

(iii) not labelled for the treatment of children 6 years or age or less; and

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

(d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient' (or words to that effect); or

(e) in other preparations **except** when included in Schedule 3 or Schedule 4.

SCHEDULE 4 – Amend Entry

PARACETAMOL:

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

(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;

(f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except when included in Schedule 2;

(g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2; or

(h) for injection.

The ACMS advised an implementation date of 1 October 2016.

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; f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Currently available to patients in packs of 100 tablets/ capsules and 50 sachets of granules. Available in packs larger than 100 tablets/ capsules.
- There is an upper limit to dosage of paracetamol, generally 4 g per day. For 500 mg tablets this represents a maximum 8 tablets/day in divided doses. Doses are generally on an "as required" basis. Other formulations of paracetamol include liquids, suppositories (Schedule 2) and injections (Schedule 4).
- There are also some products containing paracetamol in combination with other agents, (e.g. codeine, cough & cold substances) and pack size of these is controlled.
- OTC paracetamol is labelled with the required warning statements in RASML. These are:
  - Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised by a doctor.
  - If an overdose is taken or suspected, ring the Poisons Information Centre (& phone details) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.
  - Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.
- >100 tablets/capsules: to be labelled with 'For dispensing only' and 'This pack not to be supplied to a patient'.
- The potential for abuse of a substance was not applicable for single ingredient paracetamol preparations.
- Paracetamol is the most commonly taken drug in overdose.
- The UK has controls in place to limit the number of packs that can be sold at once by retail outlets (pharmacy and non-pharmacy).
- It would be useful if Australia had similar guidelines to the UK that limited the number of packs that could be sold in a single transaction and provided controls on the advertising of paracetamol products. See https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/407287/Appendix_4_-_Blue_Guide.pdf.
- There was a recent CRP determination on an advertisement for 99 cent paracetamol tablets – due to the wording of the Advertising Code section 4(2)(f), advertisements should not encourage "inappropriate or excessive use" therefore no breach could be found on the issue of encouraging inappropriate purchase due to the very low price; in this case there was a limit of three packs per transaction applied. See http://www.tgacrp.com.au/uploaded/complaints/panelDetermination/CRP%202015-02-025%20United%20Discount%20Chemists%20-%20Panamax.pdf.

The Delegate could consider liaising with the advertising unit regarding controls on advertising.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- 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 that the Schedule 2 (and Schedule 4) entry for paracetamol be amended to: (a) restrict the pack size requirements to no more than 100 tablets or capsules per pack and no more than 50 wrapped powders or sachets of granules per pack for domestic supply, and (b) specifically limit bulk pack sizes of paracetamol for supply only to hospital, nursing homes and pharmacies for dispensing purposes.

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: 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; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the decision comprised the following:

- Currently available to patients in packs of 100 tablets/ capsules and 50 sachets of granules. Available in packs larger than 100 tablets/ capsules.
- There is an upper limit to dosage of paracetamol, generally 4 g per day. For 500 mg tablets this represents a maximum 8 tablets/day in divided doses. Doses are generally on an "as required" basis. Other formulations of paracetamol include liquids, suppositories (S2) and injections (S4).
- There are also some products containing paracetamol in combination with other agents, (e.g. codeine, cough & cold substances) and pack size of these is controlled.
- OTC paracetamol is labelled with the required warning statements in RASML. These are:
  - Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised by a doctor.
  - If an overdose is taken or suspected, ring the Poisons Information Centre (& phone details) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.
  - Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.
- >100 tablets/capsules: to be labelled with 'For dispensing only' and 'This pack not to be supplied to a patient'.

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

- The potential for abuse of a substance was not applicable for single ingredient paracetamol preparations.
- Paracetamol is the most commonly taken drug in overdose.
- The UK has controls in place to limit the number of packs that can be sold at once by retail outlets (pharmacy and non-pharmacy).
- It would be useful if Australia had similar guidelines to the UK that limited the number of packs that could be sold in a single transaction and provided controls on the advertising of paracetamol products. See https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/407287/Appendix_4_-_Blue_Guide.pdf.
- There was a recent CRP determination on an advertisement for 99 cent paracetamol tablets – due to the wording of the Advertising Code section 4(2)(f), advertisements should not encourage "inappropriate or excessive use" therefore no breach could be found on the issue of encouraging inappropriate purchase due to the very low price; in this case there was a limit of three packs per transaction applied. See http://www.tgacrp.com.au/uploaded/complaints/panelDetermination/CRP%202015-02-025%20United%20Discount%20Chemists%20-%20Panamax.pdf.

The Delegate could consider liaising with the advertising unit regarding controls on advertising.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

The delegate has made a final decision that is different to the interim decision due to updates of the paracetamol entries in the June 2016 Poisons Standard. The delegate's final decision is:

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 primary pack containing no more than 12 dosage units per pack; or

b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or

c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

f) in other preparations

except:

i) when included in Schedule 3 or 4; or

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 RASML.

(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 that contains not more than 20 tablets or capsules.

(C) compliant with the requirements of the RASML.

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

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

SCHEDULE 3 - Current Entry

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

SCHEDULE 4 - Amend Entry

PARACETAMOL:

a) when combined with aspirin or salicylamide or any derivative of these substances **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;

f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;

g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;

h) for injection.

The current Appendix F entries remain appropriate.

2.5 Loratadine

Referred Delegate's scheduling proposal

Proposal to increase the pack size of unscheduled loratadine (10 mg or less) divided oral preparations from 5 dosage units to 10 dosage units when used in adults and children 12 years of age and over for the treatment of seasonal allergic rhinitis.

Applicant's application and scheduling proposal

To increase the pack size of unscheduled loratadine (10 mg or less) divided oral preparations from 5 dosage units to 10 dosage units when used in adults and children 12 years of age and over for the treatment of seasonal allergic rhinitis.

The applicant's reasons for the request were:

- To amend the current Schedule 2 and Schedule 4 entries for loratadine to have the pack size increased both entries from 5 dosage units to 10.
- Since its introduction for general sale in 2012, loratadine sales have increased by 6-fold without issue, suggesting a strong demand for the medicine outside of pharmacies for self-treatment of symptoms of rhinitis.
- Market research suggests consumers plan their allergy medication purchases in advance and furthermore suggest they require greater than 5 days' supply of loratadine.
- A larger 10 pack size aligns with consumer behaviour for accessing more than 5 days' supply, which would make it more convenient and cost effective for a consumer.
- Consumers use loratadine on an 'as needed' basis over the seasonal period of hay fever. Other 'as needed' medications, such as ibuprofen and paracetamol are available in larger pack sizes as general sales medicines.
- Symptoms of seasonal hay fever may last between 4 days to 4 weeks.
- Loratadine has minimal toxicity as compared to some analgesics.
- Loratadine has a good safety profile, a wide therapeutic index with no unusual neurological symptoms or toxicity seen in accidental overdoses. There is a low incidence of adverse reports for Loratadine. Prolonged administration of loratadine has shown no clinically significant heart complications. Loratadine has no known potential for abuse or dependency.
- Loratadine has a unique efficacy and safety profile which supports a larger pack size from non-pharmacy outlets with minimal risk.
- Internationally, countries which have an equivalent regulatory system to Australia loratadine has been approved as general sales medicine without a pack size limit or is available in a much larger pack size.

Substance summary

Loratadine is a potent, long-acting tricyclic antihistamine with selective peripheral H1-receptor antagonistic activity. Its efficacy as a first line treatment for the symptomatic treatment of allergic rhinitis and allergic skin conditions such as urticaria (hives) has long been established. Once-daily treatment as an effective control for allergic rhinitis has been available in Australia and globally for more than 20 years.

Current scheduling status

LORATADINE is currently listed in Schedules 2 and 4.

SCHEDULE 2

LORATADINE in preparations for oral use except in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

a) in a primary pack containing 5 dosage units or less; and

b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

SCHEDULE 4

LORATADINE except:

a) when included in Schedule 2; or

b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

   i) in a primary pack containing 5 dosage units or less; and

   ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

Scheduling history

At the May 1992 NDPSC meeting, the Committee recommended Loratadine be included in Schedule 4, and declined to down schedule to schedule 3 in November 1992 due to concerns about cardiac side effects.

In April 1994, the NDPSC rescheduled loratadine tablets to Schedule 3, and loratadine syrup to Schedule 3 in November 1995.

In May 1997, the NDPSC deferred a down-scheduling application for loratadine from Schedule 3 to Schedule 2, due to an article that was published in the Lancet, raising concerns of cardiovascular safety. In August 1997 meeting, the NDPSC confirmed the current Schedule 3 entry.

In February 1999, the NDPSC considered the rescheduling of loratadine from Schedule 3 to Schedule 2. The NDPSC agreed that loratadine in preparations for oral use should be rescheduled, and that the restriction to 'only therapeutically active ingredient' should no longer apply. In November 1999, the NDPSC confirmed the down-scheduling of loratadine to Schedule 2.

After discussions in February 2012, the Schedule 2 and Schedule 4 entries were amended to exempt solid dose oral preparations containing 10 mg or less of loratadine in packs containing no more than 5 dosage units for the treatment of seasonal allergic rhinitis. The exemption for treatment is for adults and children over the age of 12 years.

In July 2013, the ACMS considered a proposal to reschedule loratadine from Schedule 2 to unscheduled in oral preparations containing 10 mg or less in packs containing not more than 5 daily doses for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, with a warning label recommending a daily dose not exceeding 10 mg loratadine for adults and children with body weight over 30 kg, or recommended daily dose not exceeding 5 mg loratadine for children with body weight 30 kg and under. The Committee recommended that the current scheduling of loratadine remained appropriate, due to the risk of inappropriate use and delay in correct diagnosis, the lack of data on adverse effects/experiences/poisoning in Australia, no substantial public health benefit in exempting from schedules and a complicated dosage regimen with risk of inappropriate dosing.

Pre-meeting public submissions

Five submissions were received. Three submissions supported the proposal. The main points were:

- The safety of loratadine is well-established, there is no evidence of misuse and abuse when in Schedule 2 or unscheduled;
- Proposal that similar changes should be considered for other 2nd generation antihistamines where their exclusion from scheduling is currently limited to 5 dosage units, such as cetirizine and fexofenadine, which are of the same therapeutic class.

Two submissions opposed the proposal. The main points were:

- Increase public health risk due to lack of access to advice from a health professional, particularly for consumers that are pregnant and/or breastfeeding, using loratadine for purposes other than those described and that loratadine has potential to induce cognitive impairment and sedation.
- Small packs sufficiently accommodates the needs of consumers who may require rapid and short term relief and an increase is not warranted from a perspective of good clinical practice and optimal therapeutic outcomes.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The Committee advised that the Schedule 2 and Schedule 4 entries for loratadine be amended to increase the unscheduled loratadine dosage from 5 dosage units to 10 dosage units in divided oral preparations when used in adults and children 12 years of age and over for the treatment of seasonal allergic rhinitis. The members noted that the voluntary labelled statement to seek medical advice after 5 days of treatment is inconsistent with a 10 day pack size.

The ACMS advised an implementation date of 1 October 2016.

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

The reasons for the advice comprised the following:

- The risk of the use of the substance: not use of alternative treatments, misdiagnosis.
- The benefit of ease of accessibility, customer preference.
- Loratadine has a positive safety profile with low toxicity even at doses greater than recommended.
- Loratadine is currently available as an unscheduled pack for seasonal allergic rhinitis. It is available in a majority of similar countries overseas over the counter for seasonal allergic rhinitis. It is also available over the counter in some countries for additional indications, as well as an unrestricted pack size.
- Loratadine has a well-established toxicity profile. Post market use in Australia and overseas has shown a positive risk-benefit profile. Adverse reactions are similar to placebo and no clinically significant drug interactions are noted.
- The proposed unscheduled pack includes a dose suitable for adults and children over 12 years of age only.

The packaging and labelling for the current unscheduled pack is suitable.

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[22];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the Schedule 2 and Schedule 4 entries for loratadine be amended to increase the unscheduled loratidine dosage from 5 dosage units to 10 dosage units in divided oral preparations when used in adults and children 12 years of age and over for the treatment of seasonal allergic rhinitis.

The proposed implementation date is 1 October 2016.

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

The reasons for the advice comprised the following:

- The risk of the use of the substance: not use of alternative treatments, misdiagnosis.
- The benefit of ease of accessibility, customer preference.
- Loratadine has a positive safety profile with low toxicity even at doses greater than recommended.
- Loratadine is currently available as an unscheduled pack for seasonal allergic rhinitis. It is available in a majority of similar countries overseas over the counter for seasonal allergic rhinitis. It is also available over the counter in some countries for additional indications, as well as an unrestricted pack size.
- Loratadine has a well-established toxicity profile. Post market use in Australia and overseas has shown a positive risk-benefit profile. Adverse reactions are similar to placebo and no clinically significant drug interactions are noted.
- The proposed unscheduled pack includes a dose suitable for adults and children over 12 years of age only.
- The packaging and labelling for the current unscheduled pack is suitable.

Public submissions on the interim decision

No submissions were received.

Delegate's final decision

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

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

3. Scheduling proposals referred to the March 2016 joint meeting of the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling (ACCS-ACMS#12)

Summary of delegates' final decisions

Substance	Final Decision
SYMPHYTUM spp. (Comfrey)	**SCHEDULE 10 - Amend Entry** SYMPHYTUM spp. (Comfrey) in preparations for human or animal use **except** when in Schedule 5. **SCHEDULE 5 - Amend Entry** SYMPHYTUM spp. (Comfrey) in preparations for dermal therapeutic or dermal cosmetic use. Implementation date: 1 October 2016.

3.1 Symphytum spp. (Comfrey)

Referred Delegate's scheduling proposal

To amend the existing schedule entries for SYMPHYTUM spp. (Comfrey) to resolve ambiguity between restricted uses in Schedule 10/Appendix C and Schedule 5 entries for dermal use and use in cosmetics. It is proposed that the existing Schedule 10/Appendix C entry be amended as follows:

- SYMPHYTUM spp. (Comfrey) in preparations for internal use.

Applicant's application and scheduling proposal

Delegate-initiated application. The reasons for the request were:

- Scheduling clarification - there is ambiguity between existing entries in Schedule 5 and Schedule 10/Appendix C. It is unclear whether the existing entries reflect the intent of the Committee when existing entries were established.

The historical records associated with the development of the Schedule 5 and 10 entries for SYMPHYTUM spp. (Comfrey) refer to the various uses of comfrey and the potential for oral exposure through food and the use of traditional medicines (predominately homeopathic) as well as dermal exposure through the application of creams and ointments. The main concern appears to have been the potential hepatotoxicity of pyrrolizidine alkaloids found in SYMPHYTUM species (Comfrey). It has been noted that the limited extent of dermal absorption and systemic availability of these alkaloids when applied dermally reduces the risks of toxicity such that it is consistent with the criteria for a Schedule 5 entry. While other exposure routes and therapeutic uses have significant toxicity concerns and warrant higher restrictions via listing in Schedule 10 (then Appendix C). The resultant revised wording of the Schedule 5 and 10 entries at the May 1998 NDPSC meeting did not provide this level of clarity as to which products are covered by the two entries.

Current scheduling status

SYMPHYTUM spp. (Comfrey) is currently listed in Schedules 5 and 10/Appendix C and in Appendix F.

Schedule 10/Appendix C

SYMPHYTUM spp. (Comfrey) for therapeutic or cosmetic use except when included in Schedule 5.

Schedule 5

SYMPHYTUM spp. (Comfrey) for dermal use.

Appendix F

SYMPHYTUM spp. (Comfrey) when included in Schedule 5.

Safety directions: 31, 32

Scheduling history

SYMPHYTUM spp. (Comfrey) has been considered by previous scheduling committees on a number of occasions.

It was first considered in May 1978 to be low risk except where consumption of large quantities was involved and was not scheduled.

In November 1983, the committee noted that while human poisonings had not been recorded, comfrey contained a carcinogenic alkaloid shown to produce a cumulative toxic effect. The committee agreed to include comfrey prepared and packed for internal use in humans as a new Schedule 1 entry for comfrey of:

- COMFREY (Symphytum) being preparations and admixtures for internal use of comminuted leaves or dried and powdered root or any part of the dried plant.

In May 1992, the committee considered submissions in relation to the proposed exemption for topical applications of comfrey due to the low level of pyrrolizidine alkaloids (PAs) in the plants and the low level of dermal absorption. A 1988 review by the Commonwealth Health Department noted that "creams that contain *Symphytum officinale* extract are not considered to be a significant source of the intake of comfrey in view of the low dermal absorption of the pyrrolizidine alkaloids".

The committee considered that while theoretically an element of risk of liver damage and cancer due to low levels of exposure to PAs in man could not be denied, the likelihood following exposure to small amounts of PAs of the kind present in comfrey was extremely low, even in the case of exposure involving un-braided skin. The committee could not justify the prohibition of the use of the plant in approved external use formulations. The committee examined the list of ointment bases provided by the Traditional Medicines Evaluation Committee and considered that they would not increase the dermal absorption of comfrey to a level which would have toxicological concerns. The substance was included in Schedule 5 with two new Appendix F warnings as follows:

Appendix C

SYMPHYTUM spp. (Comfrey) for therapeutic use except when included in Schedule 5.

Schedule 5

SYMPHYTUM spp. (Comfrey) in ointments and creams for dermal use.

Appendix F, Part 3

Symphytum spp. (Comfrey) when included in Schedule 5.

Safety Directions: 31. Do not use on broken skin. 32. Do not use under occlusive dressing.

In May 1998, the committee considered a submission to allow the sale of comfrey when in dermal preparations such as sprays. It noted the Schedule 5 entry included creams and ointments for dermal use and all other therapeutic preparations were covered by the Appendix C entry.

The 1998 committee noted that at the previous consideration percutaneous absorption of comfrey, with hepatotoxic PAs was a major issue in the consideration of an exemption for comfrey in dermal

preparations. It also noted that to achieve therapeutic effects, some absorption would be required and if vehicles such as DMSO were used, enhanced absorption would be expected. The current scheduling did not preclude the use of specific vehicles and that the issue of inappropriate formulations could be an issue to be considered by the TGA at the time of registration. The committee agreed that the restriction for 'creams and ointments' should be deleted from the Schedule 5 entry. The Appendix F warning statements were considered appropriate.

The committee agreed that there was potential for confusion in the interpretation of the entries for use in cosmetics, as the Appendix C entry specifically mentioned therapeutic use, but the Schedule 5 entry did not. The committee agreed that the toxicity associated with topical comfrey in either therapeutic or cosmetic use was the same. The committee agreed the Appendix C entry should clarify that it was its intention that comfrey for cosmetic use should be controlled in the same way as therapeutic preparations.

No change was made to the Appendix F warnings. The current schedule 5 and 10 (then Appendix C) entries were set in May 1998

Pre-meeting public submissions

Three submissions were received. Two submissions supported the proposal, and one opposed the proposal.

- The first submission noted that there are a number of dermal non-prescription products (creams and ointments) entered in the ARTG contain *Symphytum officinale*, advocating that the current Schedule 5 entry for dermal preparations is appropriate, but that it may be appropriate to amend the Schedule 10 entry to ensure no ambiguity with the Schedule 5 entry.
- The second submission supported clarifying the Schedule entries. They proposed the amendment to Schedule 5 be as follows: SYMPHYTUM spp. (Comfrey) for dermal use except when included in Schedule 10.
- The third submission did not support the proposal on the grounds that natural “herb” or “organic” materials should not be banned.

Summary of ACCS-ACMS advice to the delegates

The committee agreed that the existing schedule entries were ambiguous and recommended that the Schedule 10 entry for Symphytum be amended as follows:

Schedule 10/Appendix C - Amend Entry

SYMPHYTUM spp. (Comfrey) in preparations for human or animal use **except** when in Schedule 5

Schedule 5 - Amend Entry

SYMPHYTUM spp. (Comfrey) in preparations for dermal therapeutic or dermal cosmetic use

The committee advised an implementation date of 1 October 2016 would be appropriate.

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 rectify ambiguity in current entries.

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS and ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[23];
- Other relevant information.

Delegates' interim decision

The delegates note, and accept, the advice from the joint meeting of the ACCS and ACMS, and agree to amend the current entries for *symphytum spp* (comfrey) in schedules 5 and 10. The delegates note that previous considerations by the NDPSC, in regard to the scheduling of products containing *symphytum spp,* had been mainly concerned with limiting human exposures via routes that could result in significant systemic exposures (except via food, which is not regulated by poison scheduling). The intent of the current schedule entries is to use the Schedule 5 entry to allow only certain types of dermal exposures (in therapeutic and cosmetic products applied topically). The proposed amendments aim to clarify that only topically applied therapeutic products and dermally applied cosmetics would be allowed under the Schedule 5 entry. The existing Warning Statement in Appendix F reinforces this message.

The proposed implementation date is **1 October 2016**. The proposed edits to existing entries in Schedules 5 and 10 do not constitute an intent to change the current scheduling arrangements; merely to clarify the entries. Accordingly, an early implementation date is appropriate.

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

Schedule entry

SCHEDULE 10 - Amend Entry

SYMPHYTUM spp. (Comfrey) in preparations for human or animal use **except** when in Schedule 5.

SCHEDULE 5 - Amend Entry

SYMPHYTUM spp. (Comfrey) in preparations for dermal therapeutic or dermal cosmetic use.

Public submissions on the interim decision

One submission was received. The submission commented that the current schedule entry for comfrey is not in line with international practice and requested that cosmetic uses of comfrey be excluded from scheduling. They note comfrey was initially scheduled for oral use due to hepatotoxicity concerns for pyrrolizidine alkaloids (PAs) found in comfrey, but since PAs have low dermal absorption, dermally applied medicines were eventually down scheduled to Schedule 5. They noted that the reason for not excluding dermal application of comfrey from scheduling completely was due to concerns that solvents such as dimethylsulfoxide (DMSO) may allow more PAs through the skin barrier.

The submission further noted DMSO is included in the Poisons Standard, and therefore any cosmetic use with that solvent would already bear a "POISON" label. Comfrey is allowed in cosmetics in the EU and is used as a skin conditioning agent, abrasive, soothing agent and antidandruff ingredient. DMSO

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

is banned in cosmetics in the EU. Amendment to the proposed schedule entry was proposed to reflect these concerns.

Delegates' final decision

The delegates note the submission made in relation to the interim decision that asks for cosmetic use to be excluded from the Schedule 5 entry. The submission suggests a need to align with international regulation of cosmetics but produces no evidence that the topical application of therapeutic and cosmetic products results in different risk profiles. The advice from the joint meeting of the ACCS and ACMS was that dermal application in either therapeutic or cosmetic products should carry a CAUTION label, despite the lower risk of systemic absorption of pyrrolizidine alkaloids. The delegates have therefore decided to confirm the interim decision. The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The implementation date is 1 October 2016.

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

4. Agricultural and veterinary chemicals

Summary of delegate's final decisions

Substance	Final Decision
Cyclaniliprole	**Appendix B - New Entry** CYCLANILIPROLE. Reason for listing: a (low toxicity) Area of use: 1.2 (Insecticide) Implementation date: 1 October 2016.

4.1 Cyclaniliprole

Delegate's Scheduling proposal

In April 2016 the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA), referred the following scheduling proposal to be considered by the delegate:

- A proposal to consider a positive listing of cyclaniliprole in Appendix B of the SUSMP for agricultural use, based on the low toxicity of the substance.

Applicant's application

The applicant, as part of an application to the APVMA, submitted a data package seeking approval of the new active constituent cyclaniliprole and registration of a new product ISK Cyclaniliprole 50 SL Insecticide, containing 50 g/L cyclaniliprole in a soluble concentrate formulation. Cyclaniliprole is a ryanodine receptor modulator and part of the anthranilic diamide class of chemicals. 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. The applicant for registration of the product did not propose a schedule for cyclaniliprole as part of the application.

The proposed product ISK Cyclaniliprole 50 SL Insecticide is intended to be used as an insecticide for the control of codling moth in apples.

Substance summary

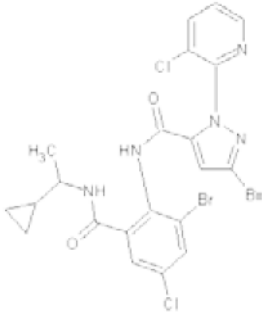

Figure 14. Chemical structure of cyclaniliprole

Acute toxicity

The acute toxicity endpoints for cyclaniliprole and ISK Cyclaniliprole 50 SL Insecticide are listed in the tables below.

Toxicity	Species	Cyclaniliprole	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat and mice	LD_{50} > 2000 (no deaths)	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} > 2000 (no deaths)	Appendix B
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	LC_{50} > 4620 (no deaths)	Appendix B
Skin irritation	Rabbit	Non-irritant	Appendix B
Eye irritation	Rabbit	Non-irritant	Appendix B
Skin sensitisation	Guinea pig (GPMT) Mouse (LLNA)	Non-sensitiser	Appendix B

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

Toxicity	Species	ISK Cyclaniliprole 50 SL Insecticide
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} > 2000 (no deaths)
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} > 2000 (no deaths)
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	LC_{50} > 5050 (no deaths)
Skin irritation	Rabbit	Non-irritant
Eye irritation	Rabbit	Slight irritant
Skin sensitisation	Guinea pig (Buehler) Mouse (LLNA)	Non-sensitiser

The change in eye irritation potential for ISK Cyclaniliprole 50 SL Insecticide is likely due to the product excipients rather than the active constituent.

Repeat-dose toxicity

Low systemic toxicity effects were observed with cyclaniliprole in all dietary studies in rats and mice. Dogs appeared to be the more sensitive species compared to rodents, with relatively low NOAELs (~4 mg/kg bw/d) based on toxicologically significant changes in liver weights and clinical chemistry (notably ALP and albumin levels) at higher dose levels.

No treatment related adverse effects were seen in a short-term rat dermal study at the limit dose.

Genotoxicity and mutagenicity

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

Carcinogenicity

No increased incidence was seen in any tumour type in male or female mice in a 78-week dietary study or in male or female rats in a 2-year dietary study.

Reproduction and developmental toxicity

There was no evidence of reproductive or developmental toxicity in the two-generation reproduction study in rats, or in the developmental studies in rats and rabbits.

Neurotoxicity and immunotoxicity

No evidence of an acute neurotoxic effect was observed in functional observation battery or motor activity assessment in the acute and repeat dose neurotoxicity studies at or up to limit dose of cyclaniliprole.

Cyclaniliprole was not immunotoxic in female mice.

Observation in humans

No information was provided.

Public exposure

No information was provided.

International regulations

Cyclaniliprole is currently under consideration by EFSA, US EPA and Health Canada. No published regulatory decisions from these agencies have been found as of the preparation of this paper, though EFSA has undertaken a public comment process in 2015 on a draft assessment report for cyclaniliprole.

Scheduling status

CYCLANILIPROLE is not specifically scheduled.

Scheduling history

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

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B entry for cyclaniliprole as follows:

Appendix B - New Entry

CYCLANILIPROLE

Reason for listing: a (low toxicity)

Area of use: 1.2 (Insecticide)

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

The reasons for the interim decision comprised the following:

- The OCS evaluation suggests a low toxicity profile for the specific product that does not meet any of the SPF criteria for listing in the Schedules.
- It meets criteria for a positive listing in Appendix B of the SUSMP for agricultural use, based on its low toxicity.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- OCS evaluation report
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[24];
- Other relevant information.

Submissions on the interim decision

The applicant had no objections to the Delegate's interim decision.

Delegate's final decision

The delegate notes the submission from the applicant supporting the interim decision. The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision. The implementation date is 1 October 2016.

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

5. New Chemical Entities – medicines for human therapeutic use

Summary of delegates' final decisions

Substance	Final Decision
Ixekizumab	**Schedule 4 - New Entry** IXEKIZUMAB. Implementation date: 1 October 2016
Phleum pratense extract	**Schedule 4 - New Entry** PHLEUM PRATENSE POLLEN EXTRACT (Timothy-grass pollen extract). Implementation date: 1 October 2016
Velpatasvir	**Schedule 4 - New Entry** VELPATASVIR. Implementation date: 1 October 2016
Follitropin delta	**Schedule 4 - New Entry** FOLLITROPIN DELTA. Implementation date: 1 October 2016
Deoxycholic acid	**Schedule 4 - New Entry** DEOXYCHOLIC ACID. Implementation date: 1 October 2016
Pirfenidone	**Schedule 4 – New Entry** PIRFENIDONE. Implementation date: 1 October 2016

5.1 Ixekizumab

Delegate's Scheduling proposal

The delegate considered an application from the TGA for the scheduling of ixekizumab, a new chemical entity for a human therapeutic medicine.

Substance summary

Ixekizumab is a humanised monoclonal antibody against the pro-inflammatory cytokine interleukin-17A (IL-17A).

Ixekizumab is indicated for the treatment of adult patients with moderate to severe plaque psoriasis.

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Ixekizumab is not specifically scheduled and is not captured by any entry in the current *Standard for the Uniform Scheduling of Medicines and Poisons*.

Delegate's interim decision

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework scheduling factors;
- The TGA evaluation report;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include ixekizumab in Schedule 4, with an implementation date of 1 October 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance; (b) the purpose 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 delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical or marketing experience in Australia.
- The product suppresses the immune system and requires ongoing monitoring for infection and other serious side effects.
- Product is administered via subcutaneous injection.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

IXEKIZUMAB.

5.2 Phleum pratense extract

Delegate's Scheduling proposal

The delegate considered an application from the TGA for the scheduling of *Phleum pretense* extract, a new chemical entity for a human therapeutic medicine.

Substance summary

Phleum pratense extract is a standardised allergen extract of grass pollen from Timothy-grass (Phleum pratense).

Phleum pratense extract is indicated for:

- allergy immunotherapy indicated for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis;
- disease-modifying treatment of grass pollen induced rhinitis and conjunctivitis; and
- use in persons aged 5 years or older.

Scheduling status

Phleum pratense extract is not specifically scheduled and is not captured by any entry in the current *Standard for the Uniform Scheduling of Medicines and Poisons*.

Delegate's interim decision

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Delegate's considerations

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework scheduling factors;
- The TGA evaluation report;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include *Phleum pratense* extract in Schedule 4, with an implementation date of 1 October 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; (c) the toxicity of a substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical experience in Australia.
- It is an allergy immunotherapy indicated for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis; It is to be prescribed by medical practitioners.
- The product can cause severe anaphylactic reactions including anaphylactic shock.
- It is an oral tablet, and the initial treatment should only be undertaken under medical supervision.
- After taking the tablet, patients require to be monitored for half an hour at a medical facility.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

PHLEUM PRATENSE POLLEN EXTRACT (Timothy-grass pollen extract).

5.3 Velpatasvir

Delegate's Scheduling proposal

The delegate considered an application from the TGA for the scheduling of velpatasvir, a new chemical entity for a human therapeutic medicine.

Substance summary

Velpatasvir is a novel pan-genotypic HCV non-structural protein 5A (NS5A) inhibitor for use in combination with sofosbuvir for the treatment of HCV infection.

Velpatasvir, in a fixed combination with sofosbuvir, is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Scheduling status

Velpatasvir is not specifically scheduled and is not captured by any entry in the current *Standard for the Uniform Scheduling of Medicines and Poisons*.

Delegate's interim decision

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Delegate's considerations

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework scheduling factors;
- The TGA evaluation report;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include velpatasvir in Schedule 4, with an implementation date of 1 October 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance; (b) the purpose 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 delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical/marketing experience in Australia or overseas.
- Treatment of hepatitis C infection.
- Limited data from the clinical trials base.

- Needs to be consistent with the other direct acting antiviral drugs for use in the treatment of hepatitis C infection.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

VELPATASVIR

5.4 Follitropin delta

Delegate's Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of follitropin delta, a new chemical entity for a human therapeutic medicine.

Substance summary

Follitropin delta is a novel human recombinant follicle-stimulating hormone (rhFSH) intended for controlled ovarian stimulation (COS) in women undergoing assisted reproductive technology (ART) therapy such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

Follitropin delta is indicated for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle.

Scheduling status

Follitropin delta is not specifically scheduled and is not captured by any entry in the current *Standard for the Uniform Scheduling of Medicines and Poisons*.

Delegate's interim decision

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Delegate's considerations

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989;*
- The Scheduling Policy Framework scheduling factors;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include follitropin delta in Schedule 4, with an implementation date of 1 October 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* is (a) the risks and benefits of the use of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical/marketing experience in Australia.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

FOLLITROPIN DELTA

5.5 Deoxycholic acid

Delegate's Scheduling proposal

The delegate considered an application from the TGA for the scheduling of deoxycholic acid, a new chemical entity for a human therapeutic medicine.

Substance summary

Deoxycholic acid is a an adipocytolytic drug, which when injected into localized subcutaneous fat, physically disrupts the cell membrane of adipocytes and causes adipocytolysis, the destruction of fat cells.

Deoxycholic acid is indicated for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

Scheduling status

Deoxycholic acid is not specifically scheduled and is not captured by any entry in the current *Standard for the Uniform Scheduling of Medicines and Poisons*.

Delegate's interim decision

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Delegate's considerations

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework scheduling factors;
- The TGA evaluation report;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include deoxycholic acid in Schedule 4, with an implementation date of 1 October 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* is (a) the risks and benefits of the use of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical/marketing experience in Australia.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

DEOXYCHOLIC ACID.

5.6 Pirfenidone

Delegate's Scheduling proposal

The delegate considered an application from the TGA for the scheduling of pirfenidone, a new chemical entity for a human therapeutic medicine.

Substance summary

Pirfenidone exerts both anti-fibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin- and transplant induced fibrosis). IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β) and the substance has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Pirfenidone is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Scheduling status

Pirfenidone is not specifically scheduled and is not captured by any entry in the current *Standard for the Uniform Scheduling of Medicines and Poisons*.

Delegate's interim decision

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Delegate's considerations

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework scheduling factors;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include pirfenidone in Schedule 4, with an implementation date of 1 October 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* is (a) the risks and benefits of the use of a substance.

The delegate decided that the reason for the final decision comprises the following:

- It is a new chemical entity with no [clinical/marketing] experience in Australia.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

PIRFENIDONE.