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

July 2015

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

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

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the March 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#13);
- 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 29 January 2015 and the second public notice was published on 4 June 2015 at Consultation Invitation for March 2015 meeting and March 2015 Delegate's Interim Decisions and Consultation Invitation, respectively.

Edited versions of the public submissions received in response to the invitation were published on 4 June 2015 at http://www.tga.gov.au/scheduling-submission/public-submissions-scheduling-matters-referred-accs13-march-2015

Interim decisions

The delegate's interim decisions on recommendations by the ACCS#13 were published on 4 June 2015 at http://www.tga.gov.au/scheduling-decision-interim/reasons-scheduling-delegates-interim-decision-and-invitation-further-comment-accs-june-2015. 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 were published on 23 July 2015 and are available at Chemical Scheduling Submissions.

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, 2010), available at Scheduling Policy Framework.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the Poisons Standard are published electronically on ComLaw. Further information, including links to the Poisons Standard on ComLaw, is available at Poisons Standard.

Privacy and your personal information

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

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

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

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

The Department's privacy policy is available at: Department of Health Privacy Policy. Alternatively you may contact the Department by telephone on (02) 6289 1555 or freecall 1800 020 103, or by using the online inquiries form at Department of Health.

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
CAS	Chemical Abstract Service

Abbreviation	Name
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 for Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation

Abbreviation	Name
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
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])

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

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

Table of contents

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

1. Scheduling proposals referred to the March 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#13)

SUMMARY OF DELEGATE'S FINAL DECISIONS

Substance	Final Decision
2-ethylhexanoic acid and its derivatives	Pending
2-hydroxyethyl methacrylate	**Schedule 5 – New Entry** 2-HYDROXYETHYL METHACRYLATE **except** when in nail preparations labelled "Avoid contact with skin" **Appendix E, Part 2 – New Entry** 2-HYDROXYETHYL METHACRYLATE Standard statements A, E1, S1. **Appendix F, Part 3 – New Entry** 2-HYDROXYETHYL METHACRYLATE - warning statement 28, safety direction 4. Implementation date – 1 February 2016
4,5-dichloro-2-N-octyl-3(2H)-isothiazolone	Pending
4,7-methano-1H-indene-5-acetaldehyde, octahydro-	Not to schedule
4-aminopropiophenone	**Schedule 7 – New Entry** 4-AMINOPROPIOPHENONE **Appendix J, Part 2 – New Entry** 4-AMINOPROPIOPHENONE Standard statement 3. Implementation date – 1 October 2015.
Ammonium cocoyl isethionate	**Schedule 6 – New Entry** AMMONIUM COCOYL ISETHIONATE, **except** in cosmetic rinse-off preparations containing 30 per cent or less and if containing more than 5 per cent of ammonium cocoyl isethionate when labelled with a warning to the following effect:

Substance	Final Decision
	IF IN EYES WASH OUT IMMEDIATELY WITH WATER **Appendix E, Part 2 – New Entry** AMMONIUM COCOYL ISETHIONATE Standard statement E1. Implementation date – 1 February 2016
Babassuamidopropyl betaine	***Schedule 6 – New Entry*** AMIDOPROPYL BETAINES **except:** (a) in cosmetic wash-off preparations containing 30 per cent or less of amidopropyl betaines and, if containing more than 5 per cent of amidopropyl betaines when labelled with a warning to the following effect: IF IN EYES WASH OUT IMMEDIATELY WITH WATER; (b) in cosmetic leave-on preparations containing 1.5 per cent or less of amidopropyl betaines. (c) in other preparations containing 30 per cent or less of amidopropyl betaines and, if containing more than 5 per cent of amidopropyl betaines, when labelled with warnings to the following effect: IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER. **Appendix E, Part 2 – New Entry** AMIDOPROPYL BETAINES · in cosmetic wash-off preparations when included in Schedule 6 Standard statement E1 · in other preparations when included in Schedule 6 Standard statements E1 and S1 Implementation date – 1 February 2016
Flupyradifurone	**Schedule 6 – New Entry** FLUPYRADIFURONE Implementation date – 1 October 2015
Metofluthrin	***Schedule 5 – Amendment***

Substance	Final Decision
	METOFLUTHRIN, – in impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk; or – when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin for use as a mosquito repellent. Implementation date – 1 October 2015

1.1.2-HYDROXYETHYL METHACRYLATE

Scheduling proposal

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

· A proposal to create a new entry for 2-hydroxyethyl methacrylate in Schedule 5 for use in cosmetics or domestic products.

The reasons for the request were:

· Uses of the chemical in Australia at concentrations up to 10 % in cosmetic products and up to 80 % in domestic products have been identified through Safety Data Sheets (SDSs). Overseas information confirms the use of the chemical in cosmetics (25 products in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 2011) and domestic products (Household Products Database, US Department of Health and Human Services).

· The main route of public exposure is expected to be through the skin, although the rate of polymerisation would be expected to limit the extent of exposure. When used in nail enhancement products, short-term small volume skin contact in the immediate vicinity of the fingernail may occur. Exposure is considered more probable for home use of the chemicals than in salon use by trained personnel. Dermal exposure to other parts of the body may occur during domestic use. The low volatility of the chemical limits the potential for exposure through vapour inhalation.

· Skin sensitisation may occur following exposure to the chemical and other structurally related methacrylates (cross–sensitisation). The CIR advised that methacrylate ester monomers ‘are safe to use in nail enhancement products when skin contact is avoided. Products containing these ingredients should be accompanied with directions to avoid skin contact, because of the sensitising potential of methacrylates’ (CIR, 2005).

· There are currently no labelling requirements for products containing this chemical in Australia. Therefore, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk under the uses identified.

· The chemical may be present in nail enhancement products as a residual monomer (at <1% on the polymer weight) in polymers based on this chemical, and the proposal is not intended to affect the use of such polymers, as the total residual monomer content of the product is expected to be very low in such cases.

Delegate's reasons for referring this to the committee

The toxicological issue (sensitisation potential) raised in relation to the use of 2-hydroxyethyl methacrylate in nail hardening preparations is similar to that considered in relation to the existing Schedule 5, 6 and Appendix C entries for ethyl and methyl methacrylate. It also raises similar considerations to hydroxypropyl methacrylate that were considered by the ACCS in July 2014. It would therefore be reasonable to make a delegate-only decision to make a similar listing in Schedule 5 (viz. 2-HYDROXYETHYL METHACRYLATE in nail preparations **except** when labelled 'avoid contact with skin'). However, the delegate notes that there are potentially products in the domestic market that may contain much higher concentrations of 2-hydroxyethyl methacrylate (up to 70-80% in windshield repair kits; 10-30% in adhesives/sealants). Therefore, referral to the ACCS is indicated to provide advice on the scheduling of products likely to contain such high concentrations.

The delegate asked the committee the following questions:

- Are there sufficient similarities between the toxicological profiles of the methyl, ethyl, 2-hydroxypropyl and 2-hydroxyethyl esters of methacrylate to use current schedule entries as a template? Methyl methacrylate is currently listed in Schedule 6, with exemptions for preparations containing 1% or less, and for cosmetic use (but note that cosmetic uses of methyl methacrylate are proscribed via listing in Appendix C). Ethyl methacrylate is listed in Schedule 5, but only for cosmetic use and is exempt from scheduling in preparations containing 1% or less. In July 2014, the ACCS recommended a similar Schedule 5 entry for 2- hydroxypropyl methacrylate:
  2-HYDROXYETHYL METHACRYLATE in nail preparations **except** when labelled 'avoid contact with skin'

- Noting that the key toxicological issue with the use of 2- hydroxyethyl methacrylate in nail hardeners (sensitisation potential and cross-sensitisation with other methacrylates) is similar to that previously considered; does the ACCS support a similar scheduling approach for 2-hydroxyethyl methacrylate in nail hardener preparations?

- What scheduling consideration is needed for products potentially containing high concentrations of 2-hydoxyethyl methacrylate (70-80% in windscreen repair kits; 10-30% in adhesives & sealants)?

- Note that the Minutes of the February 2007 meeting of the National Drugs and Poisons Scheduling Committee (NDPSC) include a detailed discussion of the rationale for setting a 1% exemption for both methyl and ethyl methacrylates. Is such an exemption cut-off also appropriate for 2-hydroxeythyl methacrylate?

Would the ACCS propose suitable entries in Appendices E & F?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *2-propenoic acid, 2-methyl-, 2-hydroxyethyl ester*. This report is publicly available on the NICNAS website: NICNAS IMAP-assessment ID 1187.

Acute toxicity

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

Toxicity	**Species**	**2-hydroxyethyl methyacrylate**	**SPF Classification**

Acute oral toxicity LD_{50} (mg/kg bw)	Rats and mice	>2000	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits	>2000	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	No data	-	-
Skin irritation	Rabbits	Slight irritant (limited data) (R38 in HSIS)	
Eye irritation	Rabbits	Moderate irritant (R36 in HSIS)	
Skin sensitisation (Magnusson and Kligman maximisation test)	Guinea pigs	Positive in 9/12 guinea pigs (No LLNA data; R43 in HSIS)	

Scheduling status

2-Hydroxyethyl methacrylate is not specifically scheduled.

Scheduling history

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

However, this substance belongs to a group of chemicals known as methacrylate esters, and other chemicals in this group have been considered by NDPSC and ACCS, for the same use and due to the same hazardous property of skin sensitisation. Two other chemicals belonging to this group of chemicals, namely ethyl methacrylate and methyl methacrylate are listed in the Poisons Standard. The NDPSC considered these two chemicals several times over the period of 2006-2008. The committee decided to include ethyl methacrylate in Schedule 5 at concentrations above 1% as the low irritancy and skin sensitisation risks of ethyl methacrylate could be appropriately reduced through including a new Schedule 5 entry for cosmetic use and to create an Appendix F entry providing appropriate warning statements and safety directions and that these risks are sufficiently reduced when there is ≤ 1% monomer present as a residue in a polymer as to warrant exclusion from the requirements of scheduling.

The committee decided to include methyl methacrylate in Schedule 6 for non-cosmetic uses at concentrations above 1% and Appendix C for all cosmetic uses. The committee noted that the severe dermal irritancy, moderate respiratory irritancy and evidence of moderate sensitising potential of methyl methacrylate constituted a moderate potential for causing harm (when for non-cosmetic uses), the extent of which could be reduced through the use of appropriate packaging and labelling and that these risks are sufficiently reduced when there is ≤ 1% monomer present as a residue in a polymer as to warrant exclusion from the requirements of scheduling. However, the cosmetic use of MMA posed sufficient danger as to warrant prohibition of sale, supply and use through inclusion in Appendix C

Another methacrylate ester, 2-hydroxypropyl methacrylate, was considered by the ACCS in July 2014. The delegate's decision was to add the substance to Schedule 5 in nail preparations **except** when labelled 'avoid contact with skin'. The delegate noted the toxicity of 2-hydroxypropyl methacrylate appears to be less severe than the methyl- and ethyl-methacrylates

currently listed in Schedule 5, 6 and Appendix C, although there is some potential for cross-sensitisation to occur between these methacrylate derivatives when used in nail preparations. The implementation date for this decision is 1 January 2016.The final decision of 2-hydroxypropyl methacrylate is available at https://www.tga.gov.au/book/final-decisions-matters-referred-expert-advisory-committee-11-14#1.4.

Schedule 5

ETHYL METHACRYLATE (excluding its derivatives) for cosmetic use **except** in preparations containing 1 per cent or less of ethyl methacrylate as residual monomer in a polymer.

Schedule 6

† METHYL METHACRYLATE (excluding its derivatives) **except**:

- for cosmetic use; or
- in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

Schedule 10/Appendix C

METHYL METHACRYLATE for cosmetic use **except** in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

Appendix F, Part 3

Poison	**Warning Statements**	**Safety Direction**
Ethyl methacrylate	28. (Over) (Repeated) exposure may cause sensitisation.	4. Avoid contact with skin. 9. Use only in well ventilated area. 23. Keep away from heat, sparks and naked flames.

Appendix F, Part 3

Poison	**Warning Statements**	**Safety Direction**
Methyl methacrylate	28. (Over) (Repeated) exposure may cause sensitisation.	4. Avoid contact with skin. 9. Use only in well ventilated area. 23. Keep away from heat, sparks and naked flames.

Pre-meeting public submissions

One submission was received, which was not in support of scheduling. The submission noted that there are no restrictions on the use of the substance in cosmetics internationally, that a CIR expert review panel concluded that the methacrylate esters considered are safe as used in nail enhancement

products when skin contact is avoided, and there has been no demonstration of harm from the use of the substance in Australia or in other economies with comparable safety standards.

Edited versions of these submissions are available at Public submissions on matters referred to the March 2015 meeting .

Summary of ACCS advice to the delegate

The committee recommended that a new Schedule 5 entry be created for 2-hydroxyethyl-methacrylate except when in nail preparations labelled "Avoid contact with skin"

The committee also recommended appropriate Appendix E statements (standard statements A, E1 and S1) and F statements (warning statement 28, safety direction 4) for 2-hydroxyethyl methacrylate.

The committee recommended an implementation date of 1 February 2016.

The committee also recommended that the delegate consult with the Medicines Scheduling Delegate on dental restorative preparations containing 2-hydroxyethyl methacrylate ethyl.

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

The reasons for the recommendations comprised the following:

- Risks associated with the use pattern in nail preparations can be managed with appropriate labelling.
- Skin sensitisation potential and evidence of eye irritation.

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;
- Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that a new Schedule 5 entry be created for 2-hydroxyethyl methacrylate. Its toxicological profile is consistent with the SPF criteria for Schedule 5, including relatively low acute toxicity, skin/eye irritancy and sensitization potential. The toxicity of 2-hydroxyethyl methacrylate appears to be less severe than the methyl- and ethyl-methacrylates currently listed in Schedule 5, 6 and Appendix C, although there is some potential for cross-sensitization to occur between these methacrylate derivatives when used in nail preparations. The delegate notes, and accepts, ACCS advice that the entry should not be specific for its use in cosmetic products because of its potential use in other products at high concentrations, but that products used on the cuticles (nails) could be exempted with appropriate 'reverse scheduling' label warning statement '*avoid contact with skin*'. The delegate also notes that the potential for use of 2-

hydroxyethyl methacrylate in dental restorative products and has referred the matter to the medicines delegate for consideration.

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.

The delegate agrees with the proposed implementation date of 1 February 2016. An extended implementation date should allow sufficient time for existing affected products to be re-labelled or withdrawn.

Public submissions on the interim decision

One submission was received on the delegate's interim decision. That submission did not object to the delegate's interim decision.

An edited version of the submission is available at Public submissions on scheduling matters.

Delegate's Final Decision

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

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

Schedule 5 – New Entry

2-HYDROXYETHYL METHACRYLATE **except** when in nail preparations labelled "Avoid contact with skin"

Appendix E, Part 2 – New Entry

Poison	**Standard statements**
2-hydroxyethyl methacrylate	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 – If in eyes wash out immediately with water S1 – If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Appendix F, Part 3 – New Entry

Poison	**Warning statements**	**Safety direction**
2-hydroxyethyl methacrylate	28. (Over) (Repeated) exposure may cause sensitisation.	4. Avoid contact with skin.

1.2 4,7-METHANO-1H-INDENE-5-ACETALDEHYDE, OCTAHYDRO-

Scheduling proposal

In December 2014, the 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 4,7-Methano-1H-indene-5-acetaldehyde, octahydro- in Schedule 6 when used in cosmetic and household products, except when used in accordance with the NICNAS recommended usage concentrations.

The reasons for the request were:

- The chemical has moderate to high acute oral toxicity, consistent with the Schedule 6 factors
- The chemical is a skin irritant and skin sensitiser, consistent with the Schedule 6 factors

The chemical has been early listed on to the Australian Inventory of Chemical Substances (AICS) at the request of the notifier and is therefore currently available for use by introducers other than the original notifier.

Based on the outcomes of a quantitative risk assessment (sensitisation) the recommended usage concentration in fine fragrances is lower than that initially proposed for use by the notifier. All other concentrations are those proposed by the notifier and found to not pose an unreasonable risk based on the NICNAS assessment. The assessment noted the absence of hazard data to assess the chronic toxicity of the notified chemical. This was deemed important in the context of the acute toxicity of the notified chemical. In the absence of repeat dose data, the notified chemical was approved for use in cosmetic and household products based on the limited exposure potential, as reflected in the very low use concentrations.

Delegate's reasons for referring this to the committee

The ACCS has now considered a number of fragrance chemicals referred from the NICNAS. For chemicals with a low toxicity profile and likely to be present at quite low concentrations in products in the retail market, the ACCS has advised that there is insufficient public health risk to warrant inclusion in a schedule of the Poisons Standard. At the November 2014 ACCS, there were five fragrance chemicals that generated such advice. At the November 2013 and July 2014 ACCS meetings, similar advice was offered in relation to two other fragrance ingredients. However, at the July 2014 meeting, ACCS advice in relation and one other fragrance chemical (*4,4-dimethyl-1-cyclohexene-1 propanal*) was to list it is Schedule 6, with exempt cut-offs at 0.1% to 1% for various cosmetic and other product types. The different ACCS advice appears to be related to the severity of the toxicity potential of the pure compound, with *4,4-dimethyl-1-cyclohexene-1 propanal* recommended a Schedule 6 listing because of the severity of the skin/eye irritancy potential and sensitization potential.

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the toxicological profile of of 4,7-Methano-1H-indene-5-acetaldehyde, octahydro- is sufficiently similar to the seven fragrance chemicals where no scheduling action was recommended, or is it more like 4,4-dimethyl-1-cyclohexene-1 propanal, where listing in Schedule 6 was recommended, along with different product-related exemption cut-offs?
- If scheduling is recommended, is the chemical name (*4,7-Methano-1H-indene-5-carboxaldehyde, octahydro-6-methyl-*) or the name used in the NICNAS assessment (*4,7-Methano-1H-indene-5-acetaldehyde, octahydro*) the preferred name for listing (or some other name)?

Does the ACCS support different exempt cut-offs for a Schedule 6 entry for different product types, as proposed in the NICNAS report?

Substance summary

Please refer to the NICNAS New Chemical assessment report for 4,7-Methano-1H-indene-5-acetaldehyde, octahydro- . This report is publicly available on the NICNAS website: NICNAS report.docx.

Acute toxicity

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

Toxicity	**Species**	**4,7-Methano-1H-indene-5-acetaldehyde, octahydro-**	**SPF Classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	300-2000	Moderate to high toxicity
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	In-vitro	Irritant	
Eye irritation	In-vitro	Non-irritant	
Skin sensitisation (LLNA)	Mouse	Sensitiser (EC3 = 7.13%)	
Skin sensitisation	Human	Non-sensitiser	

Repeat-dose toxicity

No information was provided.

Mutagenicity

This substance was not a mutagenic in bacterial reverse mutation test.

Genotoxicity

This substance was not clastogenic in *in vitro* test.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 0.5% concentration) through the use of a wide range of cosmetic and household products. The principal routes of exposure will be dermal, while ocular and inhalation exposures (e.g. through the use of spray products) are also possible.

International regulations

No information was provided.

Scheduling status

4,7-Methano-1H-indene-5-acetaldehyde, octahydro- is not specifically scheduled.

Scheduling history

4,7-Methano-1H-indene-5-acetaldehyde, octahydro- has not been previously considered for scheduling; therefore, scheduling history is not available.

However, a chemical with a similar toxicological profile, namely 4,4-dimethyl-1-cyclohexene-1-propanol was considered by the ACCS in March 2014 and the Delegate decided in his final decisions to include this chemical in Schedule 6.

Schedule 6 – New Entry

4,4-DIMETHYL-1-CYCLOHEXENE-1-PROPANAL **except**:

- in leave-on cosmetic preparations containing 0.1 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal;
- in rinse-off cosmetic preparations containing 0.5 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal; or
- in other preparations containing 1 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal.

Appendix E, Part 2 – New Entry

Poisons	**Standard statements**
4,4-Dimethyl- 1-cyclohexene-1-propanal	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E2 - If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.

Appendix F, Part 3 – New Entry

Poisons	**Warning statements**	**Safety direction**

Poisons	Warning statements	Safety direction
4,4-Dimethyl-1-cyclohexene-1-propanal	5. Irritant. 28. (Over) (Repeated) exposure may cause sensitisation.	1. Avoid contact with eyes. 2. Avoid contact with skin.

Pre-meeting public submissions

One submission was received, which did not support scheduling. The submission notes the history of not scheduling fragrances and notes that there is an international standard (International Fragrance Association, IFRA) that applies to fragrances that companies internationally comply with.

Summary of ACCS advice to the delegate

The committee recommended that 4,7-Methano-1H-indene-5-acetaldehyde, octahydro- does not require a schedule listing.

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; and (c) the toxicity of a substance.

The reasons for the recommendation comprised the following:

- Use as a fragrance in low concentrations.
- Use in low concentrations and alternative controls warrants leaving this product unscheduled.

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[1];
- Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient 4,7-methano-1H-indene-5-acetaldehyde, octahydro- does not require scheduling. The delegate notes that sensitisation potential is the toxicological finding that could justify inclusion in the schedules, and that the ACCS has made recommendations at this and previous meetings that it is not necessary to use the

[1] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [Scheduling Policy Framework]

scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the Poisons Standard.

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

Public submissions on the interim decision

One submission was received. The submission supported the delegate's interim decision.

An edited version of the submission is available at Public submissions on scheduling matters.

Delegate's final decision

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

1.3 4-AMINOPROPIOPHENONE

Scheduling proposal

In January 2015, the OCS, based on an application made to the APVMA to register a new active constituent and new products for agricultural uses, referred the following proposal to be considered by the chemicals scheduling delegate:

- That a new entry for 4-aminopropiophenone be created in Schedule 7

The reasons for the request are discussed below.

A toxicological data package has been submitted to support the approval of a new active constituent, 4-aminopropiophenone (also known as para-aminopropiophenone, or PAPP) for agricultural use. A concurrent application by a separate applicant seeks registration of new products relying on the active constituent data submitted. One product (wild dog bait) contains 1.68% PAPP, while another (fox bait) contains 1.14% PAPP. The products are intended for use as vertebrate toxins for the population control of wild dogs and foxes respectively.

The OCS notes that this is the first consideration of PAPP for agricultural use.

Delegate's reasons for referring this to the committee

The delegate asked the committee the following questions:

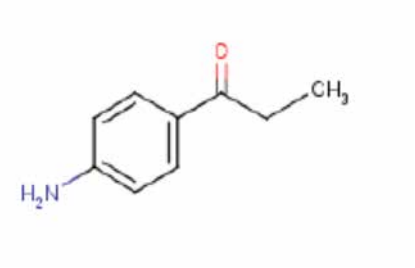
- The proposed use pattern of this pesticide is as a wild dog/ fox bait. The OCS report notes that the lethal dose in the dog (30-50 mg/kg) is much lower than in rodents (170-230 mg/kg). While the dog LD_{50} falls within the range the SPF suggests for listing in Schedule7, the rodent acute lethality is more in the range the SPF suggests for Schedule 6, and this is the basis that the product sponsor has argued for a listing in Schedule 6.

- The OCS supports its recommendation for listing in Schedule 7 by noting that humans are relatively more susceptible to methaemoglobinaemia, the key toxic effect caused by PAPP, and that the overall toxicity profile is based on relatively old and non-compliant toxicity studies. Furthermore, there is some evidence of PAPP's genotoxicity potential and inadequate evidence to establish its carcinogenicity potential.

- Does the ACCS support listing 4-aminopropiophenone in Schedule 7 or in Schedule 6, with or without a low-level cut-off? Should this listing include an index cross-reference to PAPP?
- Does the proposed use pattern suggest listing in Appendix J, noting that such listing is reserved only for substances also listed in Schedule 7?

Substance summary

PAPP is an anticyanide drug based on its methaemoglobin forming mode of action.



Structure of 4-aminopropiophenone

Acute toxicity

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

Toxicity	**Species**	**PAPP**	**SPF Classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Dog Rat Mouse	30-50 177-221 168-223	High to extreme high toxicity Moderate to high toxicity Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	No data	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	No data	No data	N/A
Skin irritation	No data	No data	N/A
Eye irritation	No data	No data	N/A
Skin sensitisation	No data	No data	N/A

The acute toxicity end-points for the two products are listed in the below tables.

Toxicity	**Species**	**Product**	**SPF Classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Estimated from available data	Low toxicity (LD_{50} > 1731/1322 mg/kg bw)[#]	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Estimated/inferred from data	Likely to be low toxicity (dermal pharmacokinetics study	N/A

Toxicity	Species	Product	SPF Classification
		with product)	
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	No data	No data	N/A
Skin irritation	No data	No data	N/A
Eye irritation	No data	No data	N/A
Skin sensitisation	No data	No data	N/A

[#] *The estimation in this case* was by Finney's estimation, assuming PAPP acute oral LD_{50} of 30 mg/kg bw and assigning an oral LD_{50} of 5000 mg/kg bw for the balance of non-active constituents in this case for the purposes of the calculation, noting that while no LD_{50} data were available for the non-active constituents, the non-active constituents are in general use as food and/or food additives).

Toxicokinetics/ADME

In experimental animals including dogs, rats and monkeys, PAPP is absorbed by gastrointestinal tract more rapidly in rats and dogs (T_{max} up to 60 min) than in monkeys (Tmax 1 – 1.5 hour). Urine is the major pathway of excretion (> 70% administered radiolabel), and faeces is the minor elimination route in these species.

The oral bioavailability of PAPP in dogs was reported at 32-52%, while an early study reported information that 65-90% of an orally administered 1.25 mg/kg bw dose of PAPP in humans was accounted for in urine samples.

PAPP is biotransformed by the liver enzymes *in vivo* into a bioactive form, as the hydroxylamine derivative PHAPP. Once formed, PHAPP is taken up by circulating erythrocytes where a redox cycle, known as *kreisprozess*, taken place, where PHAPP is converted to p-nitrosopropiophenone (PNPP), which brings about the simultaneous oxidation of haem Fe^{2+} to Fe^{3+}. Intra-erythrocytic NADPH, generated from glucose-6-phosphate dehydrogenase, participates in the reduction of p-nitrosopropiophenone (PNPP) back to PHAPP, which again can oxidize a haem portion of the haemoglobin (Hb) molecule to methaemoglobin (MetHb).

Repeat-dose toxicity

Two short term toxicology studies for PAPP were presented for evaluation: a 14-day oral study in rats, and a 14-day oral study in monkeys. No observed effect levels (NOELs) were not established in the studies.

In the 14-day rat study, PAPP was administered at 0, 35 / 20, 90 / 50 or 140 / 130 mg/kg bw/d (for M/F respectively). Enlarged spleens associated with erythroid hyperplasia, sinusoidal enlargement and pigment, and raised MetHb were observed in all dose levels, which led to a LOEL of 35 mg/kg bw/d in males and 20 mg/kg bw/d in females. In addition, reduced RBC count along with increased PCV and haemoglobin were evident at ≥90/50 mg/kg bw/d; pigment was also present in Kupffer cells of the liver and renal proximal tubular epithelial cells at the high dose level.

In the 14-day monkey study, PAPP was administered at 0, 17, 50 and 150 mg/kg bw/d, and a LOEL was established at 17 mg/kg bw/d on the basis of raised MetHb concentrations detected before dosing each day, RBC morphology and bone marrow changes and Heinz body formation in all test groups during the dosing period. These changes were not fully reversed after a 2-week recovery

period. In both studies, the haematology data indicated the effects of PAPP on erythropoiesis, along with oxidative damage and haemolysis.

No other repeat-dose studies were provided in the submission.

Mutagenicity/genotoxicity

PAPP was positive for mutagenicity in an Ames test (+S9). Summary data suggested that PAPP was mutagenic in the presence of S9 metabolic activation in the forward gene mutation assay.

Two *in vivo* mouse micronucleus tests were provided in the submission. In the first study, PAPP (unpurified; unknown purity/concentration) elicited a negative clastogenicity response, while in the second study, PAPP (>100% purity from the certificate of analysis) was considered to induce micronuclei in bone marrow (i.e. elicited clastogenic potential), as the definition of a negative clastogenic response was not met.

The OCS notes that no primary guideline-compliant *in vitro* genotoxicity data was provided in the submission, and the available *in vivo* micronucleus test data raises concerns regarding the *in vivo* clastogenic potential of the test (supported by the Ames test data). On this basis, the OCS considers that PAPP is likely to be genotoxic.

Carcinogenicity

Overall, from the information available, it is unknown whether PAPP is carcinogenic. Secondary data of limited reporting and regulatory value suggested that PAPP induced an increased incidence of tumours and carcinomas, while another study indicated that PAPP did not trigger treatment-related changes in neoplastic observations in a methylcholanthrene model of epidermal tumourigenesis.

Reproduction and developmental toxicity

No data on reproduction and developmental toxicity were available.

Other toxicology endpoints

Overall, there is insufficient data to determine whether PAPP has neurotoxic or immunotoxic potential.

Observation in humans

PAPP was well absorbed in the human following ingestion of 1.25 mg/kg bw, and 65 – 90% of the administered dose was accounted for in the urine.

PAPP given orally to human volunteers at 50, 80 or 100 mg (equivalent to 1.1 – 1.8 mg/kg bw PAPP) resulted in a maximum MetHb level of 7% (n = 1), 13.1% (range 0 – 43%, n = 37) and 22% (range 2 – 48%, n = 13) respectively. MetHb formation began 15–30 minutes after PAPP treatment, and peak levels were reached at 1–2 hours after PAPP treatment. The high variability in the maximum MetHb level within a dose group was likely related to differences in body weights and the contents of the gastric compartments, noting that fasting resulted in higher peak MetHb formation upon PAPP dosing. Other than bluish lips, the study did not note any clinical signs or other adverse effects associated with PAPP-induced methaemoglobinaemia.

Single oral doses of PAPP caused increases of MetHb levels in a dose-related manner in one normal female human subject, i.e. 3.5% and 15% MetHb after 1.14 and 3.4 mg/kg bw PAPP doses respectively (n = 1 only). In addition, two males showed higher responses to PAPP, with 24% and 32% MetHb formation after 1.45 and 1.39 mg/kg bw PAPP doses respectively.

A number of general clinical review papers discussing methaemoglobinaemia indicated that sustained high MetHb levels ≥ 20% resulted in a range of clinical symptoms/signs with scaling MetHb levels, including headache, dyspnoea, nausea and tachycardia occurring at ≥20% MetHb; lethargy, stupor and deteroriating consciousness occurring at up to 55% MetHb; cardiac arrhythmias, circulatory failure and neurological depression at ≥ 55% MetHb, and death/mortality occurring at ~70% MetHb.

It is noted that the information derived was mostly limited to single dose exposures at low dose levels (0.7 - 1.8 mg/kg bw). Even at this low dose range, PAPP caused a clear dose-related increase in MetHb levels in human subjects (up to 48%), suggesting that humans are sensitive to PAPP-mediated MetHb formation and the likely effects associated with elevated MetHb levels described in clinical reviews discussing methaemoglobinaemia.

Public exposure

Occupational use considerations

The use pattern for the PAPP products is similar to existing registered meat based baits, such as 1080 baits.

Both dog and fox baits are applied at a rate of one bait per 5 – 10 ha (only one bait per site), up to 20 baits per km^2 depending on dog and fox densities. One bait is sufficient to kill a wild dog or a fox.

The baits will be applied predominantly into pastoral farming areas to target wild dogs and foxes preying on livestock, and also in national parks and other crown land where wild dogs and foxes require management.

Based on the formulation (a solid bait matrix) and product use pattern, dermal contact with the products baits will be the main route of exposure for users.

The European Union has recently published a HEEG opinion on a harmonised approach for the assessment of rodenticides (EC, 2012) which provides guidance on the use rates and exposure for rodenticides based on an exposure study. This guidance has been used by OCS along with the provided draft product label indications and applicant information in the absence of product specific data. The most appropriate scenario for pre-formed baits would be wax blocks in this case, though it is acknowledged that the wax block scenario described is a slightly conservative estimate.

The relevant endpoint for risk assessment was methaemoglobin formation observed across studies (noted as a toxicodynamic effect of PAPP administration). The LOEL of 0.8 mg/kg bw was selected for the risk assessment, and the MOE applicable to this risk assessment was identified as 100, consisting of a 10-fold intra-species variation, a two-fold safety factor for use of a LOEL, and a 5-fold safety factor for deficiencies in the PAPP database in this case.

Overall exposure to PAPP arising from application of the products is 222.32 mg of product per day (equivalent to 0.2 g of product per day).

Based on a concentration of 1.68% PAPP in the wild dog bait and an average weight of an adult of 70 kg, this would result on a systemic exposure of 0.053 mg PAPP/kg bw/d without gloves, and a systemic exposure of 0.0053 mg PAPP/kg bw/d with gloves. (Given the lower content of PAPP in fox bait, and the identical use pattern, the modelling for fox bait was not conducted in full as the exposure estimate for wild dog bait was considered sufficient).

Comparison of the risk assessment endpoint LOEL with the expected daily exposure to the product, indicates that the MOE for use of the product when wearing a single latery of clothing is 15 without gloves, and 151 with gloves. This indicates that there is an adequate MOE for the product to be used

according to the described use pattern with the use of appropriate PPE (use of single-layer of clothing and chemical-resistant gloves).

Public health considerations

From a public exposure viewpoint, in the incidental contact and accidental ingestion scenario, a 10 kg toddler consuming a whole bait would result in a systemic exposure equivalent to 40–100 mg/kg bw PAPP.

In considering the toxicology of PAPP and PAPP-induced methaemoglobin formation, the available toxicity data indicates that relatively low doses of PAPP (approximately 0.8 mg/kg bw) would produce methaemoglobin in humans, albeit at relatively low levels (4.5–12%; see Paulet *et al.,*1963), with no clinical signs of toxicity observed. The data also shows a steep dose response curve for methaemoglobin formation. In addition, reported acute oral LD_{50} values after ingestion of PAPP were 30–50 mg/kg bw in dogs, and 177–221 mg/kg bw in rats (though rats are not regarded as adequately predicting the acute oral toxicity potential of PAPP in humans). Therefore, it is noted that the resulting oral exposure to PAPP after accidental ingestion of a bait (40–100 mg/kg bw for a toddler) would not result in a sufficient margin of safety.

In this case, noting that the product is not intended for domestic use, this risk of accidental ingestion of a bait by a toddler may be further mitigated by the addition of label warning statements and restraints limiting access to the products, and warning the general public when baiting operations are taking place, in a similar manner to that for other bait products such as 1080-based products (noting that uneaten bait will also be collected by workers after expiration of the baiting period). The following label restraints/statements are recommended:

- Not for domestic use.
- Keep out of reach of children

In addition, the proposed RLP leaflet from the applicant contains language regarding public notification, poison notices and distance restrictions which are considered appropriate and should be retained.

> **PUBLIC NOTIFICATION**
>
> *While fox PAPP baits (400mg PAPP baits) pose a lower risk to dogs, the PAPP dose in wild dog baits (1000mg PAPP) will kill any dog. Neighbours should be notified to allow them to take appropriate action. The notification should advise that steps (e.g. restraint, muzzling) need to be taken to ensure that domestic dogs do not gain access to PAPP baits. The notification should specify the dates between which baiting will occur. This notification should be given to all adjoining landholders at least 72 hours in advance. A record of the notifications should be kept. If baiting is not undertaken within the dates specified an additional notification should be made.*
>
> **POISON NOTICES**
>
> *Signage is compulsory for all lands where baiting occurs. Do not lay baits until signage is in place. Signage must include – date baits laid, contact numbers, toxin name (PAPP), target animal and a warning that domestic animals and pets can be affected. Users must ensure that signs are put up before baiting with this product commences on the property and are placed according to requirements specified by the relevant State/Territory authority. These notices must remain up for at least 4 weeks after the authorised period of bait lay has expired or after all untaken baits have been collected.*
>
> **DISTANCE RESTRICTIONS**
>
> *It is important to reduce risks of accidental poisoning of working and pet dogs. Baits must be placed at least 150m from a dwelling; 20m from permanent or flowing water bodies; 5m from boundary fences; and 5m from the edge of formed public roadways.*

International regulations

A risk assessment on PAPP was conducted by New Zealand EPA in 2011, supporting the distribution of PAPP baits for vertebrate pest control.

Scheduling status

4-Aminopropiophenone (para-aminopropiophenone or PAPP) is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

Three submissions were received.

One submission supported a Schedule 7 listing of PAPP active constituent and other formulations above 1000 mg total PAPP in a single package. However, the submission proposed a cut-off to Schedule 6 in baits with 1000 mg PAPP or less.

One submission notes that foxes and wild dogs are an increasing problem in Australian and the impact on the goat industry has been catastrophic in some areas; and PAPP is a very viable and much safer alternative to 1080 poison commonly used for baiting. Therefore, the submission notes PAPP must be listed as a schedule 6 not a schedule 7 poison.

One submission supported PAPP technical material being listed in Schedule 7 (i.e. PAPP technical active and pre-formulated PAPP concentrate), but strongly submit that manufactured bait products containing PAPP do not present a significant public health risk and belong in Schedule 6. They noted that PAPP bait products belong in Schedule 6 because:

- they satisfy the criteria for Schedule 6 and fail the criteria for Schedule 7 set out in the published scheduling factors, and
- they have an effective antidote to administer in the event of accidental consumption, which is consistent with Schedule 6 and comparable to other poison baits e.g. snail and slug baits that are generally included in a lower Schedule 5 category.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended inclusion of 4-aminopropiophenone in S7 with cross referencing in the index to para-aminopropiophenone (PAPP).

The committee also recommended the following Appendix J, condition 3, Part 1 entry:

4-Aminopropiophenone - Not to be used except by or in accordance with the directions of accredited government vermin control officers

The committee supported the implementation to occur as soon as possible.

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

The reasons for the recommendation comprised the following:

- Toxicity consistent with Schedule 7
- Can be presented in a way that poses a clear risk

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 accepts the advice from the ACCS and agrees to include a new entry for 4-aminopropiophenone in Schedule 7, with a cross-reference in the Poisons Standard index to the common name, para-amidopropiophenone (PAPP).

The toxicity profile of the active ingredient is consistent with SPF criteria for listing in Schedule 7, including an LD_{50} estimate in dogs at 30-50 mg/kg, positive evidence of genotoxicity potential, and indeterminate evidence relating to its potential carcinogenicity. The delegate notes the submissions that have argued for creating an exception to Schedule 6 for the formulated bait products, but accepts ACCS advice that such an exception is not warranted on grounds of toxicity and the potential for a toddler to be seriously poisoned through consumption of complete bait. The delegate notes that repeated dose studies with PAPP failed to demonstrate a no observed adverse effect level (NOAEL) at the lowest doses tested (17-20 mg/kg/d) and that humans may be even more susceptible to methaemoglobinaemia formation, possibly at doses as low as 0.1-1.8 mg/kg.

The delegate also notes advice from ACCS members that access controls available through listing in Schedule 7 and Appendix J are required for use in jurisdictions where the products are likely to be used. The delegate notes that such controls would also complement the stated intention of the APVMA to regulate the products as *Restricted Chemical Products*.

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

The Appendix J entry proposes that the States/Territories impose use controls consistent with other vertebrate pest controls.

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[2] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [Scheduling Policy Framework]

The delegate agrees that the earliest date for implementation of the scheduling decision is desirable to allow the States/Territories to exert appropriate controls as soon as the product registration occurs. The proposed implementation date is 1 October 2015.

Public submissions on the interim decision

No public submissions were received before the due date.

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

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

Schedule 7 – New Entry

4-AMINOPROPIOPHENONE

Appendix J, Part 2 – New Entry

Poison	**Standard statements**
4-Aminopropiophenone	3 - Not to be used except by or in accordance with the directions of accredited government vermin control officers

1.4 AMMONIUM COCOYL ISETHIONATE

Scheduling proposal

In December 2014, the 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 Ammonium Cocoyl Isethionate in Schedule 6 when used in cosmetic products, except when used in rinse-off cosmetic products at ≤ 10% concentration.

The reasons for the request were:

· The notified chemical is a severe eye irritant, consistent with Schedule 6

· The notified chemical has only been assessed for use in rinse-off cosmetic products

The proposed concentration cut-off of 10% is the concentration proposed by the notifier as their intended maximum use concentration. The NICNAS assessment determined that there was no unreasonable risk to the public when used at up to 10% in rinse-off cosmetic products.

Delegate's reasons for referring this to the committee

The delegate asked the ACCS the following questions:

· The NICNAS assessment report notes that, while the acute toxicity of ammonium cocoyl isoethionate is quite low, there is some potential for skin irritancy and potentially severe eye irritancy. This toxicity profile is typical of an anionic detergent substance and it appears to be more consistent with SPF criteria for listing in Schedule 5, rather than the proposed Schedule 6.

- Should a listing be made under the specific salt name AMMONIUM COCOYL ISOETHIONATE (the INCI name) or a more generic name, such as Fatty acids, coco, 2-sulfoethyl esters, ammonium salts?
- The NICNAS report concludes that "*the risk to the public associated with the use of the notified chemical at ≤ 10% in rinse off cosmetic products is not considered to be unreasonable*". Is this a suitable cut-off concentration for exemption from any schedule listing?
- The ASCCS considered a similar NICNAS referral at the November 2013 meeting (cocoyl glycinate). At that time, the recommended scheduling action was create a Schedule 6 entry for cocoyl glycinate, with an exemption at less than 5% and a label requirement *If in eyes wash out immediately with water* when in leave-on preparations between 5 and 30%. In addition, the delegate proposed a First Aid entry in Appendix E mandating a label direction *If in eyes wash out immediately with water.* Is this a suitable template for listing ammonium cocoyl isoethionate?

Substance summary

Please refer to the NICNAS New Chemical assessment report for Ammonium Cocoyl Isethionate. This report is publicly available on the NICNAS website: NICNAS final report

A CIR report for isethionate salts (a group containing the notified chemical) is available (CIR, 2013). This review does not contain test data on ammonium cocoyl isethionate. The available data in the review on sodium cocoyl isethionate indicates that in studies in rabbits using concentrations of 2.5% -49% it was a mild to primary ocular irritant, and that is was defined as an ocular irritant at concentrations ≥ 15%. The review concludes that this group of isethionate salts (including the notified chemical) are safe in the present practices of use and concentrations in cosmetics, when formulated to be non-irritating.

The outcome of the CIR supports the conclusions reached in the NICNAS assessment regarding the eye irritation hazard, as the analogue chemical in the CIR was also found to be an eye irritant and the conclusion of safety for this group was on the condition that the cosmetics containing these chemicals were formulated to be non-irritating.

Acute toxicity

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

Toxicity	**Species**	**Ammonium Cocoyl Isethionate**	**SPF Classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	None
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	None
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Not provided	Not provided	-
Skin irritation	Rabbit	Slight irritant	
Eye irritation	Rabbit	Severe Irritant	

Toxicity	Species	Ammonium Cocoyl Isethionate	SPF Classification
Skin sensitisation (GPMT)	Guinea pig	Non-sensitiser	

Repeat-dose toxicity

A 28 day repeat dose study by oral gavage was conducted in rats with the notified chemical at dose levels of 15, 150 and 1000 mg/kg/day. Animals treated with a dose of 1,000 mg/kg bw/day had a range of clinical signs, a significantly elevated monocyte count, and a number of treatment related effects in the stomach including gastritis, acanthosis of the forestomach and hyperkeratosis of the forestomach. These effects were considered to be adverse and hence the lower concentration of 150 mg/kg bw/day was established as the NOAEL for systemic toxicity, based on the absence of effects at this dose.

Mutagenicity

Ammonium cocoyl isethionate was not mutagenic in a bacterial reverse mutation test (in the presence or absence of metabolic activation).

Genotoxicity

Ammonium cocoyl isethionate was not clastgenic in an *in vitro* mammalian chromosome aberration test.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤10% concentration) through the use of body and hair cleansing products. The principal route of exposure will be dermal, while oral and ocular exposure is also possible.

The notified chemical was found to cause serious eye damage when administered to rabbits at a concentration of approximately 30% and is slightly irritating to the skin. However, as the notified chemical will be present in cosmetic products at concentrations ≤ 10%, skin and eye irritation effects are expected to be reduced. The notified chemical is also proposed to be used only in rinse off cosmetic products, further reducing the potential for exposure.

The potential systemic exposure to the public from the use of the notified chemical in cosmetic products was estimated to be 0.90 mg/kg bw/day. Using a NO(A)EL of 150 mg/kg bw/day, which was derived from a 28 day repeated dose toxicity study on the notified chemical, the MOE was estimated to be 167. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences; therefore, the MOE is considered to be acceptable.

As the notified chemical may also increase the dermal absorption of other components of cosmetic products, due to its surfactant nature, care should be taken when reformulating the notified chemical into the end-use products.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 10% in rinse off cosmetic products is not considered to be unreasonable.

International regulations

No information was provided.

Scheduling status

Ammonium cocoyl isethionate is not specifically scheduled.

Scheduling history

Ammonium cocoyl isethionate has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One submission was received, which did not support scheduling. The submission noted their long held view that surfactants do not require scheduling, and that cocoyl isethionates are used as milder alternatives to lauryl sulfates.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended a new Schedule 6 entry be created for ammonium cocoyl isethionate except in preparations containing 5 per cent or less.

Schedule 6 – new entry

Ammonium cocoyl isethionate, **except** in cosmetic rinse-off preparations containing 30 per cent or less and if containing more than 5 per cent of ammonium cocoyl isethionate when labelled with a warning to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER

The committee also recommended an Appendix E entry as follows:

Appendix E, Part 2 – New Entry

Poison	**Standard Statement**
Ammonium cocoyl isethionate	E1 - If in eyes wash out immediately with water

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendation comprised the following:

- Severe eye irritation potential.

- Only rinse-off cosmetic products have been specified to date.

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 accepts ACCS advice that a new entry be created in Schedule 6 for ammonium cocoyl isethionate, with appropriate exemption cut-offs for products with low concentrations.

The delegate notes that, while the toxicity of the substances in this category meet SPF criteria for listing in Schedule 6, based on severe eye irritancy potential, their widespread use in cosmetic products, particularly shampoos, suggests they can be used safely at low concentrations in products with appropriate safety directions to wash product from the eyes. The ACCS has now considered a number of similar surfactant substances and the scheduling recommendations are consistent with the need to provide appropriate label warnings to protect against eye damage, while exempting from scheduling many products currently on the Australian market containing low substance concentrations, provided they carry the appropriate label warning statements. One submission noted that surfactant substances used in cosmetics generally do not require controls imposed via scheduling. The delegate rejects that proposal and instead accepts ACCS advice that inclusion in Schedule 6 in a manner consistent with other surfactants is more appropriate. The recently promulgated scheduling of a related compound (cocoyl glycinate) was used as a template. The proposed wording allows for low-concentration exemptions for rinse-off products, and exemption from most scheduling controls for other products subject to 'reverse labelling' with appropriate warning statements and safety directions. The ACCS noted that there was insufficient information to determine an appropriate exemption cut-off for leave-on cosmetic products, so these would be captured by the Schedule 6 listing.

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

The delegate agrees with the proposed implementation date of 1 February 2016. An extended implementation date should allow sufficient time for existing affected products to be re-labelled or withdrawn.

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[3] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [Scheduling Policy Framework]

Public submissions on the interim decision

One submission was received. The submission had no objection to the delegate's interim decision.

An edited version of the submission is available at Public submissions on scheduling matters.

Delegate's final decision

The delegate notes the submission received in response to publication of the interim decision and, in particular, the points made repeatedly in public submissions that scheduling controls over surfactant substances in cosmetics and consumer products are not appropriate. The delegate rejects that view and confirms the interim decision as no evidence has been received to alter the interim decision, noting that it is consistent with scheduling controls applied to other surfactant chemicals and provides for exemptions from other scheduling controls when appropriate label warnings are used on products. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

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

Schedule 6 – New Entry

AMMONIUM COCOYL ISETHIONATE, **except** in cosmetic rinse-off preparations containing 30 per cent or less and if containing more than 5 per cent of ammonium cocoyl isethionate when labelled with a warning to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER

Appendix E, Part 2 – New Entry

Poison	**Standard statements**
Ammonium cocoyl isethionate	E1 - If in eyes wash out immediately with water

1.5 BABASSUAMIDOPROPYL BETAINE

Scheduling proposal

In September 2013, the NICNAS proposed 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts, which is also known as babassuamidopropyl betaine for scheduling. The substance was considered by the ACCS in its July 2014 meeting together with another 1-propaniminium compound. The ACCS recommended that 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) and 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C_{8-18} and C_{18}-unsaturated acyl derivatives, inner salts), meet the factors of the Scheduling Policy Framework for including them in the generic Schedule 5, Schedule 6 and Appendix E entries for quaternary ammonium compounds. A separate listing in the Schedules is, therefore, not required for these substances.

A public submission received for the delegate's interim decision in October 2014 requested consideration of a separate schedule entry for amidopropyl betaines. The submission noted that:

- the delegate's interim decision on 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) (OR stearoxypropyltrimonium chloride) may fit the typical description of a quaternary ammonium compound. However, this is not the case for 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsaturated acyl) derivatives, inner salts (OR babassuamidopropyl betaine) and other amidopropyl betaines.

- chemically, these two substances fit into different categories: stearoxypropyltrimonium chloride is a cationic surfactant (like most quaternary ammonium compounds); babassuamidopropyl betaine, like other amidopropyl betaines, is a zwitterionic surfactant (ie a neutral molecule). While amidopropyl betaines contain a quaternary ammonium segment within the molecule and may be described by some as a quaternary ammonium compound, it also contains an organic acid segment and may be described as an organic acid. Amidopropyl betaines are used in cosmetics as a milder substitute for sodium lauryl sulfates and sodium lauryl ether sulfates, and provide similar foaming properties as these substances.
- it would be more appropriate to schedule amidopropyl betaine in a separate schedule entry, with controls that are aligned with lauryl sulfates; this approach would address the concerns regarding some existing products that may become scheduled (S5), noting that due to the differences in chemistry of amidopropyl betaines from typical quaternary ammonium compounds, these may not have been considered quaternary ammonium compounds by some in industry. Separate scheduling would align with the Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products which concluded that household laundry and cleaning products containing cocamidopropyl betaines raise no safety concerns for the consumers. The Cosmetics Ingredient Review has noted that amidopropyl betaines are safe for use in cosmetics if they are formulated to be non-sensitising (noting that sensitisation potential was likely due to an impurity rather than the substance itself).

The submission requested consideration of the following separate schedule entry for amidopropyl betaines to align with lauryl sulfate. This schedule entry allows higher concentrations of the surfactant in wash-off preparations (than quaternary ammonium compounds), while decreasing the amount allowed in leave-on preparations.

Schedule 6

AMIDOPROPYL BETAINES **except:**

- in cosmetic wash-off preparations containing 30 per cent or less of amidopropyl betaine and, if containing more than 5 per cent of amidopropyl betaine, when labelled with a warning to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

- in cosmetic leave-on preparations containing 1.5 per cent or less of amidopropyl betaine.

- in other preparations containing 30 per cent or less of amidopropyl betaine and, if containing more than 5 per cent of amidopropyl betaine, when labelled with warnings to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

  IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

The delegate noted the submission received, determined in his final decisions to set aside the interim decision for 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salt and to seek further advice from the ACCS on whether the proposed Schedule 5 entry for amidopropyl betaines is a better way to manage the scheduling of this group of zwitterionic detergents.

Delegate's reasons for referring this to the committee

This substance was referred to the July 2014 meeting of the ACCS, under the name *1-Propanaminium, 3-amino-n-(carboxymethyl)-n,n-dimethyl-, n-(c8-18 and c18-unsatd. Acyl) derivs.,*

inner salts. The ACCS was asked whether the substance would be captured under the generic Schedule 6 entry for QUATERNARY AMMONIUM COMPOUNDS. During the consultation phase on the delegate's interim decision, an industry submission suggested that this compound did not share many of the toxicological characteristics of quaternary ammonium compounds and like other amidopropyl betaines, is a neutral zwitterionic surfactant, whereas the quaternary ammonium compounds are cationic surfactants.

Accordingly, the scheduling proposal to be considered by the committee at the March ACCS meeting is to develop a generic Schedule 6 entry for AMIDOPROPYL BETAINES, or a specific entry for babassuamidopropyl betaine.

The committee should also consider exemption cut-offs for different types of cosmetic and other products, along with appropriate label first aid statements if the products make eye or skin contact.

Substance summary

Please refer to the NICNAS New Chemical Assessment Report for 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts. This report is publicly available on the NICNAS website: NICNAS Final Report.

The reasons for the original scheduling request were:

- Skin and eye irritation data indicate 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts is a slight to moderate irritant and meets the Scheduling Policy Framework's Schedule 5 criteria.
- The assessment indicated that the risk of adverse effects from repeated exposure to the chemical at no more than 6% in rinse-off products and 2% in leave-on products is considered to be acceptable.
- The risk of skin sensitisation from impurities was considered acceptable based on the probability of very low concentrations of impurities.
- As toxicity data were not provided, 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts cannot be classified according to the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004). However, based on the information available, the 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts should be considered as though it is classified with at least the following risk phrase: R36 Irritating to eyes.

Acute toxicity

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

Toxicity	**Species**	**Babassumamido propyl betaine**	**SPF classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	1800 - 5000	From low to moderate toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	2000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)		Not determined	Not determined

Toxicity	Species	Babassumamido propyl betaine	SPF classification
Skin irritation		Irritant	
Eye irritation		Severe irritant	
Skin sensitisation (LLNA, maximisation test)	Guinea pig	Sensitiser	

Repeat-dose toxicity

There are no repeat dose toxicity data on the notified chemical. In a 28-day repeated dose oral toxicity study, rats were administered a 30.6% solution of the analogue chemical at 0, 100, 500 or 1000 mg/kg bw/day. Inflammation of the non-glandular stomach was noted in animals of the high-dose group, although this effect was attributed to the irritant properties of the test material. Mortality was also observed in this study at all treatment levels but there was no dose-response relationship (CIR, 2010).

In another 28-day repeated dose oral toxicity study, rats were administered a solution containing the analogue chemical (concentration not stated) at 0, 250, 500 or 1000 mg/kg bw/day. The NOEL was reported as 500 mg/kg bw/day, which appears to be based on non-systemic irritant effects on the non-glandular stomach. No mortalities were observed (CIR, 2010).

In a 90-day repeated dose oral toxicity study, rats were administered a solution containing the analogue chemical (concentration not stated) at 0, 250, 500 or 1000 mg/kg bw/day. There were no mortalities and the noted effects are isolated to the stomach region and appear to be irritant in nature. The NOEL established by the study authors was 250 mg/kg bw/day, based on these effects (CIR, 2010).

Mutagenicity

Babassuamidopropyl betaine was not mutagenic in bacterial reverse mutation assays. Negative results were also obtained for the analogue chemical in a mouse lymphoma test and a micronucleus test in mice.

Carcinogenicity

Babassuamidopropyl betaine was not carcinogenic in 20-month dermal study using analogue chemical at concentration of 0.09% in mice.

Reproduction and developmental toxicity

No information provided.

Observation in humans

This substance was non-sensitising under the conditions of the human repeat insult patch test.

Public exposure

The general public will be repeatedly exposed to the notified chemical (at up to 6% concentration) through the use of rinse-off and leave-on cosmetic products.

International regulations

No information provided.

Scheduling status

Babassuamidopropyl betaine is not specifically scheduled; neither there is a class/group entry for amidopropyl betaines in the Poisons Standard.

Based on the recommendations made by the ACCS in July 2014 meeting, the delegate decided that another related compound, namely 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) met the factors of the Scheduling Policy Framework for including it to the generic Schedule 5, Schedule 6 and Appendix E entries for quaternary ammonium compounds. A separate listing in the Schedules is therefore not required for this substance. Scheduling history of quaternary ammonium compounds is available below under 'scheduling history'.

The public submission proposing a separate scheduling for amidopropyl betaines suggested the scheduling to align with that of similar group of chemicals, lauryl sulfates. In March 2014, the joint committee of ACCS-ACMS considered a scheduling proposal to broaden the current entry for sodium lauryl sulfate to include ammonium, potassium and sodium sulfates. The delegate made a final decision in October 2014 to amend the existing entry with the implementation date of 1 October 2015.

SCHEDULE 6 – amend entry as follows:

~~SODIUM~~ LAURYL SULFATE SALTS (excluding its ~~salts and~~ derivatives) **except**:

- in wash-off preparations containing 30 per cent or less of ~~sodium~~ lauryl sulfates and, if containing more than 5 per cent ~~sodium~~ lauryl sulfates, when labelled with a warning to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

- in leave-on preparations containing 1.5 per cent or less of ~~sodium~~ lauryl sulfates;
- in toothpaste and oral hygiene preparations containing 5 per cent or less of ~~sodium~~ lauryl sulfates;
- in other preparations for animal use containing 2 per cent or less; or
- in other preparations containing 30 per cent or less of ~~sodium~~ lauryl sulfates and, if containing more than 5 per cent ~~sodium~~ lauryl sulfates, when labelled with warnings to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

  IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

APPENDIX E, Part 2 – Amend entry to

Poison	**Standard Statement**

Poison	Standard Statement
~~Sodium~~ Lauryl sulfates · leave-on or wash-off preparations above 5 per cent	E1 – If in the eyes wash out immediately with water.
· other preparations above 5 per cent	E1 – If in the eyes wash out immediately with water. S1 – If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Scheduling history

In August 1973, the Poisons Schedule Sub-Committee decided to create a new Schedule 5 entry for preparations containing more than 10% of quaternary ammonium compounds.

In November 1997, the NDPSC decided to amend the Schedule 5 entry to include preparations containing 5 to 20% of quaternary ammonium compounds in Schedule 5 and created a new Schedule 6 entry for all other preparations containing quaternary ammonium compounds.

In November 1998, the NDPSC decided to amend the Schedules 5 and 6 entries to exempt only di-tallow dimethyl ammonium chloride was broadened to "dialkyl quaternary ammonium compounds where the alkyl groups are derived from tallow or hydrogenated tallow or similar alkyl chain length sources".

In November 2000, the NDPSC decided to exempt from scheduling all dialkoyl quaternary ammonium compounds.

Additionally, sodium lauryl sulfates (SLS) was first considered by the NDPSC in February 2010. This consideration was based on an OCS (then Office of Chemical Safety and Environmental Health (OCSEH)) evaluation report on SLS. The NDPSC generally agreed that a parent entry in Schedule 6 was appropriate for SLS given its potential for serious eye and skin irritation. The NDPSC also decided that the schedule entry should remain specific to SLS at that time. Given the widespread use of SLS in many sectors, the NDPSC indicated there would be significant potential for unintended regulatory impact from this decision. NDPSC therefore agreed that it was appropriate to foreshadow the proposed SLS scheduling for consideration at the June 2010 meeting to allow time for additional public consultation.

The NDPSC decided to foreshadow including SLS in Schedule 6 with exemptions for:

· wash-off preparations, containing 30 per cent or less of sodium lauryl sulphate;

· in leave-on preparations containing 1 per cent or less of sodium lauryl sulphate; or

· in other preparations containing 2 per cent or less of sodium lauryl sulfate.

At the meeting, the NDPSC also agreed to consider at the June 2010 meeting whether additional labelling requirements were warranted for SLS products.

In June 2010, the NDPSC generally agreed that, based on the toxicological information provided, a Schedule 6 parent entry was appropriate for SLS given its potential for serious eye irritation.

The NDPSC decided to include SLS (excluding salts and derivatives) in Schedule 6 with exemptions for:

- wash-off preparations, 30 per cent of or less;
- leave-on preparations, 1.5 per cent of or less;
- toothpaste and oral hygiene preparations, 5 per cent or less;
- in other preparations for animal use, 2 per cent or less; or
- in all remaining preparations, 30 per cent or less of sodium lauryl sulfate.

This matter was referred to the delegate for consideration under the new scheduling arrangements which commenced on 1 July 2010. The delegate agreed with the NDPSC's recommendations and decided to include these in the Poisons Standard.

In March 2011, the delegate considered SLS label warning statements and indicated that additional labelling may be required for SLS. The delegate decided to refer this matter to the joint meeting of ACCS-ACMS for advice. The delegate noted, as SLS is a severe eye and skin irritant, the label warning (for products containing greater than 5 per cent SLS) was appropriate. Based on the ACCS-ACMS advice, the delegate decided to include preparations containing more than 5 per cent of SLS in Appendix E with standard statements:

- E1 "If in eyes wash out immediately with water"; and
- S1 "If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water" for preparations which are not leave-on or wash-off preparations.

The delegate also decided to amend the Schedule 6 entry for SLS to add the following labelling criteria for products to qualify for the current exemptions from the entry:

- wash-off preparations, greater than 5 up to 30 per cent or less, are to be exempt only when labelled with a warning to the effect of "If in eyes wash out immediately with water";
- leave-on (1.5 per cent or less), toothpaste and oral hygiene preparations (5 per cent or less) and other animal use (2 per cent or less) – no additional labelling required; and
- all other preparations, greater than 5 up to 30 per cent or less, are to be exempt only when labelled with warnings to the following effect "If in eyes wash out immediately with water" and "If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water".

1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts, was considered by the ACCS in July 2014 meeting.

In December 2014, the delegate made a final decision that a separate listing for another 1-propanaminium compound, namely 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) was not required. The delegate noted, and accepted, the ACCS advice that the toxicological profile of the substance was sufficiently similar to other quaternary ammonium compounds covered by the generic listing in Schedules 5 and 6. The decision included a determination that the current cut-offs from Schedule 6 to Schedule 5 (20%) and to exempt (5%) remain appropriate for these three substances.

SCHEDULE 5

QUATERNARY AMMONIUM COMPOUNDS in preparations containing 20 per cent or less of quaternary ammonium compounds **except**:

- when separately specified in these schedules;

- dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or
- in preparations containing 5 per cent or less of such quaternary ammonium compounds.

SCHEDULE 6

QUATERNARY AMMONIUM COMPOUNDS **except**:

- when separately specified in these Schedules;
- when included in Schedule 5;
- dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or
- in preparations containing 5 per cent or less of such quaternary ammonium compounds.

APPENDIX E

Poisons	**Standard statements**
Quaternary ammonium compounds **except** when separately specified · above 20 per cent	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). G3 – If swallowed, do NOT induce vomiting. E2 - If in eyes, hold eyelids apart and flush the eyes continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.
· 20 per cent and below	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E2 - If in eyes, hold eyelids apart and flush the eyes continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.
· in pressurised spray paints	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E2 - If in eyes, hold eyelids apart and flush the eyes continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes. G6 – If sprayed in mouth, rinse mouth with water.

Pre-meeting public submissions

One submission was received, which supported the scheduling of amidopropyl betaines. The submission suggested the following entry:

Schedule 6

AMIDOPROPYL BETAINES ***except:***

- in cosmetic wash-off preparations containing 30 per cent or less of amidopropyl betaine and, if containing more than 5 per cent of amidopropyl betaine, when labelledwith a warning to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

- in cosmetic leave-on preparations containing 1.5 per cent or less of amidopropyl betaine.

- in other preparations containing 30 per cent or less of amidopropyl betaine and, If containing more than 5 per cent of amidopropyl betaine, when labelled with warnings to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

  IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

The submission did not support the scheduling of alkyl amidopropyl betaines and notes that babassuamidopropyl betaine has been used by industry to replace potentially higher risk ingredient and therefore there is a need to ensure that industry continues to have access to ingredients for innovation.

An edited version of this submission is available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended a group entry for amidopropyl betaines in Schedule 6 with exemption for preparations containing low concentrations.

Schedule 6

AMIDOPROPYL BETAINES **except:**

- in cosmetic wash-off preparations containing 30 per cent or less of amidopropyl betaines and, if containing more than 5 per cent of amidopropyl betaines when labelled with a warning to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

- in cosmetic leave-on preparations containing 1.5 per cent or less of amidopropyl betaines.

- in other preparations containing 30 per cent or less of amidopropyl betaines and, if containing more than 5 per cent of amidopropyl betaines, when labelled with warnings to the following effect:

  IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

  IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

The committee also recommended the following Appendix E, Part 2 entry:

Poison	Standard Statement
Amidopropyl betaines	
· Above 5 per cent in cosmetic wash-off preparations	E1 – If in eyes wash out immediately with water
· Above 5 per cent in other preparations	E1 – If in eyes wash out immediately with water S1 – If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

The committee recommended an implementation date of 1 February 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; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

· Does not pose same level of risk as cationic quaternary ammonium surfactants.

· Severe eye irritant.

· Widely used in cosmetics but risks can be mitigated by appropriate labelling.

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 factors4;

· Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that a new generic entry be created in Schedule 6 for amidopropyl betaines, with appropriate exemption cut-offs for products with low concentrations.

The delegate notes that, while the toxicity of the substances in this category meet SPF criteria for listing in Schedule 6, based on acute toxicity and skin/eye irritancy potential, their widespread use

[4] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [Scheduling Policy Framework]

in cosmetic products, particularly shampoos, suggests they can be used safely at low concentrations in products with appropriate safety directions to wash product from skin and/or eyes. One submission noted that this group of substances offered a milder set of irritancy properties compared with other surfactant ingredients, and that controls imposed via scheduling are not necessary. The delegate rejects that proposal and instead accepts ACCS advice that inclusion in Schedule 6 in a manner consistent with other strong surfactants is more appropriate. The proposed wording allows for low-concentration exemptions for leave-on and rinse-off products, and exemption from most scheduling controls for other products subject to 'reverse labelling' with appropriate warning statements and safety directions.

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

The delegate agrees with the proposed implementation date of 1 February 2016. An extended implementation date should allow sufficient time for existing affected products to be re-labelled or withdrawn.

Public submissions on the interim decision

One submission was received. The submission had no objection to the delegate's interim decision.

An edited version of this submission is available at Public submissions on scheduling matters.

Delegate's final decision

The delegate notes the submission received in response to publication of the interim decision and, in particular, the points made repeatedly in public submissions that scheduling controls over surfactant substances in cosmetics and consumer products are not appropriate. The delegate rejects that view and confirms the interim decision as no evidence has been received to alter the interim decision, noting that it is consistent with scheduling controls applied to other surfactant chemicals and provides for exemptions from other scheduling controls when appropriate label warnings are used on products. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

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

Schedule Entry

Schedule 6 – New Entry

AMIDOPROPYL BETAINES **except:**

(d) in cosmetic wash-off preparations containing 30 per cent or less of amidopropyl betaines and, if containing more than 5 per cent of amidopropyl betaines when labelled with a warning to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

(e) in cosmetic leave-on preparations containing 1.5 per cent or less of amidopropyl betaines.

(f) in other preparations containing 30 per cent or less of amidopropyl betaines and, if containing more than 5 per cent of amidopropyl betaines, when labelled with warnings to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

Appendix E, Part 2 – New Entry

Poison	Standard statements
Amidopropyl betaines	
· in cosmetic wash-off preparations when included in Schedule 6	E1 – If in eyes wash out immediately with water.
· in other preparations when included in Schedule 6	E1 – If in eyes wash out immediately with water. S1 – If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

1.6 FLUPYRADIFURONE

Scheduling proposal

In January 2015, the OCS, based on an application made to the APVMA to register a new active constituent, referred a proposal to create a new entry for flupyradifurone in Schedule 6 to be considered by the chemicals scheduling delegate. A product was also included in the application, and consideration of a cut-off level to exempt from scheduling for the product was also requested.

The reasons for the request are discussed below.

Flupyradifurone was the subject of a Global Joint Review evaluation between the North American Free Trade Agreement (NAFTA) agencies (US EPA, Health Canada PMRA and Mexico), Brazil and OCS. OCS was the primary evaluator for this project.

Flupyradifurone (also known as BYI 02960) is a new insecticidal compound from the butenolide chemical class. Chemicals in the butenolide family include ascorbic acid.

Flupyradifurone acts by interfering with insect nicotinic acetylcholine receptors, a class of neurotransmitter-gated cation channels which are involved in excitatory neurotransmission in the nervous system of insects. The compound acts as an agonist, leading to disorder of the nervous system and death.

Flupyradifurone is currently not listed in the Poisons Standard. The proposed product contains flupyradifurone at 200 g/L.

The scheduling considerations for flupyradifurone discussed below are based on the SPF. They take into account the toxicological profile of the chemical and the intended use patterns associated with products containing flupyradifurone as the active constituent.

OCS considers that flupyradifurone has a generally low acute toxicity profile, with the exception of slight eye irritation potential and a weak acute neurotoxicity potential following single oral gavage administration. The OCS notes that no Guideline-compliant skin sensitisation study was provided on the active constituent—the study evaluated was considered deficient, and thus no classification for skin sensitisation is possible.

The systemic findings in short-term, subchronic and chronic dietary studies were not considered to warrant scheduling, and flupyradifurone was not considered to be an in vivo genotoxicant, a

reproductive toxicant in rats, a developmental toxicant in rabbits, or an immunotoxicant in rats. Additionally, flupyradifurone was not carcinogenic in mice or rats. While not a developmental toxicant in rats, there was limited evidence of a slight developmental delay in rats exposed to maternotoxic doses (LOAEL = 150 mg/kg bw/d) of flupyradifurone. As noted above, while weak acute neurotoxicity potential was identified, neuropathology was unremarkable, and subchronic and developmental neurotoxicity studies did not report adverse neurotoxic effects.

Consideration of the SPF criteria and application of the cascading principles outlined in the SPF indicates that the active constituent flupyradifurone meets the scheduling factors for Schedule 6, with an acute oral LD50 between 300 and 2000 mg/kg bw (with reported deaths).

The product containing 200 g/L of flupyradifurone has a low acute toxicity profile, though the product elicited slight eye irritation in rabbits and the undiluted product (i.e. 100% neat form) was a dermal sensitiser in a Guideline-compliant mouse LLNA. Modelling of occupational exposure (professional use) to the active constituent from the proposed use patterns resulted in acceptable MOEs (>100) for the highest exposure scenarios without a specific requirement for protective clothing. Post-application activities were predicted to be of low risk.

In the first draft of this evaluation, the OCS noted that the product containing 200 g/L of flupyradifurone was a dermal sensitiser in a Guideline-compliant mouse LLNA, and that this would be consistent with a Schedule 6 listing (i.e. no exemptions or cut-offs are considered appropriate in this case, again noting the lack of Guideline-compliant skin sensitisation data for the active constituent flupyradifurone).

The applicant in their response to the OCS draft report in November 2014 requested that OCS recommend a Schedule 5 listing (i.e. a cut-off/exemption) for the product. This was considered by OCS and not agreed to.

On 18 December 2014, the applicant replied indicating that they had no further comment to the rejoinder and the revised draft, though they foreshadowed providing comments to the Delegate/Secretariat during an anticipated public comment phase for this application, particularly around the skin sensitisation issue.

A broad overview of the toxicology of the chemical is provided in the substance summary below.

Delegate's reasons for referring this to the committee

While the toxicological profile of flupyradifurone is relatively straightforward and could satisfy scheduling criteria for either Schedule 5 or 6, there is disagreement between the sponsor and the OCS with regard to interpretation of its sensitisation potential, and hence the appropriate schedule for the product under consideration for registration. Accordingly, the delegate sought advice from the ACCS.

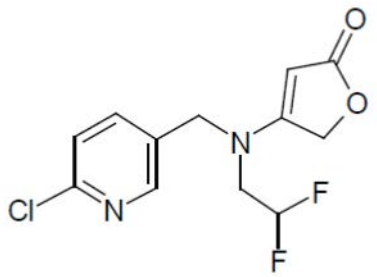
The delegate asked the committee the following questions:

- Flupyradiflurone appears to have a relatively low toxicity potential. The oral LD_{50} estimate in the range 300-2000 mg/kg is consistent with SPF criteria for listing in Schedule 6, although other aspects of the toxicology are possibly consistent with Schedule 5. The OCS evaluation has noted a non-compliant study of sensitisation potential for flupyradiflurone itself, along with a positive result in a study with the undiluted product containing 200g/L flupyradiflurone. The OCS has interpreted the sensitisation potential as 'moderate', justifying listing in Schedule 6 with no cut-off to Schedule 5, while sponsor has argued that it is 'slight'. The ACCS is requested to comment on this disparity and to recommend an appropriate schedule listing for both the active and the product.

· Are there any other elements of the toxicity evaluation likely to influence the scheduling determination?

Substance summary

Flupyradifurone belongs to the chemical class of butenolides, and acts by interfering with insect nicotinic acetylcholine receptors, a class of neurotransmitter-gated cation channels which are involved in excitatory neurotransmission in the nervous system of insects.



Structure of Flupyradifurone ($C_{12}H_{11}ClF_2N_2O_2$)

Acute toxicity

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

Toxicity	**Species**	**Flupyradifurone**	**SPF Classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	$300 < LD_{50} < 2000$ (F only)	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	$LD_{50} > 2000$ (no deaths)	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	$LC_{50} > 4671$ mg/m^3 (no deaths)	Schedule 5
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Rabbit	Slight irritation, cleared by 48 h	Schedule 5
Skin sensitisation (modified LLNA)	Mouse	N/A (study not reliable)	N/A

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

Toxicity	**Species**	**Product**	
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	$LD_{50} > 2000$ mg/kg bw (no deaths)	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	$LD_{50} > 2000$ mg/kg bw (no deaths)	N/A

Toxicity	Species	Product	
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	LC_{50} > 4483 mg/m^3 (no deaths)	Schedule 5
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (Standard LLNA)	Mouse	Sensitiser (neat formulation SI ≥ 3.0)	Schedule 5 or 6?

Toxicokinetics/ADME

In a series of seven toxicokinetic studies (e.g. absorption, distribution, metabolism and excretion (ADME) studies), flupyradifurone was rapidly absorbed and distributed throughout the body, moderately metabolised and rapidly excreted primarily *via* the urinary pathway. There was no marked sex differences in the ADME of flupyradifurone regardless of the different positions of radiolabel, with the exception of a higher proportion of C1 or C2 fragments and expired ^{14}C-carbon dioxide in males treated with [furanone-4-^{14}C]-flupyradifurone. Excretion was rapid and extensive, with the majority of the administered dose excreted within 24 hours indicating a low probability of bioaccumulation of the parent compound or metabolites. The main metabolic pathway for flupyradifurone consists primarily of hydroxylation followed by conjugation with glucuronic acid, cleavage of the difluoroethyl group forming difluoroacetic acid (DFA) and cleavage of the molecule at the pyridinylmethyl bridge, forming BYI 02960-difluoroethyl-amino-furanone.

Repeat-dose toxicity

The systemic toxicity of flupyradifurone in dietary studies consisted primarily of body weight and body weight gain decreases, liver toxicity (presenting as increased liver weight and centrilobular hepatocellular hypertrophy with associated clinical chemistry changes), and thyroid effects (e.g. follicular cell hypertrophy) generally seen at higher dose levels in rats, mice (studies over 3 months in duration) and dogs. This systemic toxicity profile was observed in short-term, subchronic and chronic toxicity studies in rats, mice and dogs, with the available data indicating that the dog was the most sensitive species. In dogs only, myofiber degeneration of skeletal muscle in both sexes was seen in the 1 year dietary study at relatively low dose levels.

No treatment related adverse effects were seen in a short-term dermal study in the rat at up to 500 mg/kg bw/d.

Mutagenicity/Genotoxicity

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 and female rats in a two year dietary study.

Reproduction and developmental toxicity

In a dietary two generation reproductive toxicity study in rats, parental systemic toxicity was seen at the top dose level (1800 ppm). Effects presented as decreased body weights seen in dams of both generations throughout pre-mating and gestation, decreased body weight gain, alterations in food

consumption, increased thyroid weight in males (both generations), and increased liver weights in males and females (both generations); however, treatment-related histopathological changes were only seen in P_1 males. Reproductive findings were also seen at 1800 ppm, including decreased litter size observed in F_2 pups, a lower number of oestrus cycles, a lower number of implantations in P_2 dams, and a slight reduction in epididymal sperm count in P_1 and P_2 males and in testicular sperm count in P_2 males was observed at 1800 ppm. In offspring, decreased pup body weight and pup body-weight gain (F_2 only) and delayed vaginal patency and preputial separation (F_1 pups only) were seen at 1800 ppm, though the slight delay in sexual maturity was considered a secondary non-specific consequence of decreased mean bodyweights in these animals.

OCS supplementary comments

In reviewing the OCS draft report, the applicant raised a disagreement with the interpretation of the parental female toxicity in the two-generation study. The applicant response is quoted below:

"[The Applicant] disagrees with the interpretation of OCS that the NOAEL for parental female toxicity was 500 ppm (minimum of 38.7 mg/kg bw/d). Although not statistically significant, declines in BW (mean decrease of -5.9%) accompanied decreases in BW gain (BWG, mean decrease of -16.3%, statistically significant) in P_1 females beginning on Day 0 and continuing throughout the premating period at this dose level. Statistically significant decreases in BW were also observed throughout gestation (mean decrease of -7.1%) and lactation (mean decrease of -7.5%), as well as for terminal BW compared to control animals. Thus, significant BW decreases were seen during all phases in F_1 generation females at 500 ppm, the same dose level that resulted in reduced F_2 pup BW late in the lactation phase (LD 14, -6.9%; LD 21, -7.4%) compared to controls. The BW decreases observed in the F_1 females were comparable in magnitude to those seen in the F_2 pups at 500 ppm. Based on these points, [the applicant] believes that the parental NOAEL should match that for the offspring."

The GJR position was that the parental NOAEL was 500 ppm, and that the body weight changes in this case were not considered a factor in the parental NOAEL selection.

The OCS re-affirms that Flupyradifurone is not considered a reproductive toxicant. However, in reviewing the argument raised by the applicant, the OCS acknowledges that there does appear to be a toxicologically significant effect at 500 ppm regarding parental female body weight and body weight gain, and notes that there appears to be some carry over effect into the second generation (particularly decreased pup weights at 500 ppm). When taken together, the OCS acknowledges that a parental toxicity effect in dams cannot be discounted, and that the parental female NOAEL in this case should be revised down from 500 ppm to 100 ppm (equivalent to a minimum of 7.7 mg/kg bw/d).

In an oral (gavage) developmental toxicity study in rats an increase in the incidence of salivation in the majority of 150 mg/kg bw/d dams was noted, along with a lower gestational bodyweight gain and statistically significant decreased food consumption. In foetuses, there were no test substance-related effects on the incidence of malformations or external variations. However, at 150 mg/kg bw/d, the incidence of the variations "parietal (unilateral/bilateral): incomplete ossification" and "hyoid centrum: incomplete ossification" were higher than in the control group and were outside the in-house historical control at both litter and foetal levels. These findings were indicative of a slightly delayed foetal development at doses where maternal toxicity was also observed. However, under the conditions of this study, the test substance did not demonstrate a teratogenic potential in the rat.

In an oral (gavage) developmental toxicity in rabbits, there was no evidence of developmental toxicity at doses up to those that produced signs of marked maternal toxicity (e.g. body weight loss

(-12% vs controls between GD 6–29)). Thus, flupyradifurone was not considered to be a developmental toxicant in rabbits.

Other toxicology endpoints

In an acute oral (gavage) neurotoxicity study in rats, a weak neurotoxic potential was seen in both sexes at ≥50 mg/kg bw, presenting as piloerection, dilated pupils, rapid respiration, lower muscle tone, low arousal, repetitive licking of lips, decreased rearing, exaggerated flexor reflexes, gait incoordination and flattened body posture, and higher incidence of tremors in both sexes on the day of administration only. However, no neuropathological changes were seen upon examination of the brain.

In a 90-day dietary neurotoxicity study, there was no evidence of neurotoxic findings during the FOB analysis or neuropathological examinations.

In a developmental neurotoxicity study, there was no evidence of neurotoxic findings during the FOB analysis or neuropathological examinations. There was a non-statistically significant increase in both motor and locomotor activity was seen in males at the high dose level that are not considered adverse.

Thus, OCS considers that the available data from the three studies only provide evidence of a weak acute neurotoxicity potential following gavage administration.

Flupyradifurone was not immunotoxic in rats.

A series of acute, repeat dose and genotoxicity studies were conducted on 4 major metabolites of flupyradifurone. The test substances included 6-chloronicotinic acid, difluroacetic acid, and BYI-02960-difluroethyl-amino-furanone, which are mammalian metabolites (rat ADME studies), phytometabolites, and were found in soils (6-chloronicotinic acid and (difluroacetic acid) and groundwater (difluroacetic acid only) in laboratory and field studies. The metabolites were either of a similar toxicity or reduced toxicity compared with the parent compound. While the metabolite BYI 02960-difluoroethyl-amino-furanone was weakly positive without metabolic activation in an *in vitro* cytogenetic assay, *in vivo* studies indicated that the substance was, on weight of evidence, not mutagenic.

Observation in humans

No information was provided.

Public exposure

No domestic (general public) exposure is expected for flupyradifurone at the time of this application. The intended use of flupyradifurone is as an insecticide on food crops. The proposed product (flupyradifurone 200 g/L) is proposed for the control of aphids, silverleaf whitefly and greenhouse whitefly in a range of vegetable crops.

Professional use exposure estimates have been modelled as part of the OCS evaluation and the product does not exceed margins of exposure that would be considered as unsafe. Risks may be mitigated by the use of the prescribed Personal Protective Equipment and adherence to the label and re-entry statements recommended.

International regulations

No specific information is available. Noting that the evaluation of this chemical was carried as a Global Joint Review collaboration, both the US EPA and Health Canada have published registration documents recently outlining their positions on flupyradifurone.

Scheduling status

Flupyradifurone is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One submission was received stating that they believe that the weight of the evidence and supporting data justify placement of formulated products containing flupyradifurone at 200 g/L into Schedule 5 of the Poisons Standard. The submission notes that the acute toxicity of the substance is low, and that the results of the dermal sensitization study support the conclusion of having very slight sensitizing potential. The submission also notes that the favourable toxicology profile of the active ingredient, flupyradifurone, further supports the formulated product as having a low health hazard and unlikely to cause harm or injury to humans.

Edited versions of these submissions are available at

Summary of ACCS advice to the delegate

The committee recommended that a new entry be created for flupyradifurone in Schedule 6.

The committee supported the implementation to occur as soon as possible.

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

The reasons for the recommendation comprised the following:

- Acute toxicity of the active and skin sensitisation of active and product is consistent with Schedule 6

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The Delegate accepts the advice from the ACCS and agrees to include a new entry for flupyridafurone in Schedule 6.

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[5] Australian Health Ministers' Advisory Council (AHMAC): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2015) [Scheduling Policy Framework]

The delegate has considered the sponsor's submission and the OCS response in relation to the sensitisation potential of the product, noting that the data in a non-compliant LLNA study submitted was inadequate to define the sensitisation potential of flupyridifurone, the active pesticide. The discussion at the ACCS was centred on whether the results of the LLNA test on the formulated product should be classified as 'moderate' or 'slight'. Moderate-severe skin sensitisation is one of the SPF criteria for listing in Schedule 6 listing and the delegate accepts the advice of the ACCS that there is sufficient doubt about whether the LLNA test results could allow the determination of a concentration cut-off to a lower schedule. Accordingly, the delegate does not propose any exception to the Schedule 6 listing of the active pesticide at this time.

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

The proposed implementation date is 1 October 2015. An early implementation date is proposed to facilitate marketing of the product when registered by the APVMA.

Public submissions on the interim decision

No public 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 reasons for the final decision are in keeping with those for the interim decision.

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

Schedule entry

Schedule 6 – New Entry

FLUPYRADIFURONE

1.7 METOFLUTHRIN

Scheduling proposal

In December 2014, the applicant via the OCS, based on an application made to the APVMA to amend the current metofluthrin entry, requested that the delegate consider amending the current entry for metofluthrin in Schedule 6 and creating a new entry for metofluthrin in Schedule 5 when impregnated into a polyethylene slow release matrix containing 212 mg or less of metofluthrin.

The reasons for the request were:

- The product has low acute toxicity via oral and dermal exposure and does not cause skin or eye irritation or skin sensitization which is consistent with Schedule 5. A risk assessment provided by the applicant demonstrated that the product has low inhalational risk to users, consistent with Schedule 5.

The Scheduling Policy Framework has been used in the consideration for inclusion of the active ingredient, metofluthrin, in Schedule 5 based on its content in the proposed product.

Delegate's reasons for referring this to the committee

At the July 2014 ACCS meeting, advice was provided to the delegate to include a new entry for metofluthrin in Schedule 5 to allow for a mosquito repellent motorised vaporiser containing metofluthrin. The current proposal seeks a further amendment to Schedule 5 to allow for

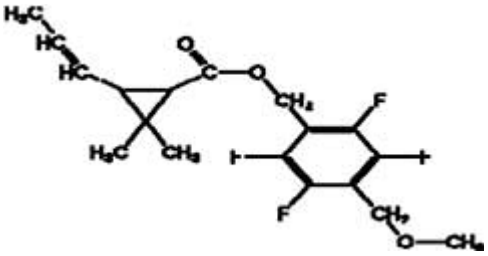
metofluthrin to be used in an impregnated woven polythene sheet. The delegate understands that previous committees (NDPSC, PSSC) have rejected applications to de-schedule mosquito nets or clothing impregnated with synthetic pyrethroid insecticides, although the ACCS recommended, in July 2013, that a mosquito net impregnated with deltamethrin should be exempted from scheduling. The July 2013 advice was based on a presumption that impregnation of the netting in a factory would be less hazardous than do-it-yourself treatment of mosquito nets with liquid insecticides. This current application appears to be different in that the size of the polythene sheet (8 x 15 cm) is too small to function as a mosquito net and that it will be enclosed in a plastic frame to minimise skin contact or ingestion potential. The mosquito repellent and knock-down properties of the product appear to rely on airflow over the fabric to release metofluthrin.

The delegate asked the ACCS the following questions:

- Does the ACCS support inclusion of a clause in the Schedule 5 entry for metofluthrin allowing for this use of the specified product? Does the proposed wording give effect to this proposal or is more specific wording required?
- Is the ACCS satisfied that the inhalation risks have been appropriately evaluated and that packaging/labelling of the product provides for sufficient mitigation of inhalation risks, and that the risks of skin contact or sucking of the material by small children is negligible?

Substance summary

Metofluthrin is a pyrethroid ester. This class of chemicals act on the nervous system of insects, disturbing the function of neurons by interacting with sodium channels.



Structure of metofluthrin.

Acute toxicity

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

Toxicity	**Species**	**Metofluthrin**	**SPF Classification**
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	>1080 and ≤ 1960	Moderate to high toxicity
Skin irritation	Rabbit	Slight irritant	
Eye irritation	Rabbit	Non-irritant	

Toxicity	Species	Metofluthrin	SPF Classification
Skin sensitisation (Guinea Pig Maximisation Test)	Guinea Pig	Non-sensitiser	

The applicant has provided an acute oral and an acute dermal study in rats as well as a skin irritation study in rabbits and a skin sensitisation study in guinea pigs on the formulated product. The applicant did not provide an acute inhalational toxicity study or an eye irritation study on the formulated product. The applicant has argued that the product consists solely of metofluthrin impregnated in an inert net; therefore, the toxicology of the end-use product is the same as that of the active constituent. Therefore the acute inhalational toxicity of the product and the eye irritation potential is based on the toxicity of the active.

The acute toxicity of the product forming the basis for the current scheduling proposal is included in the table below:

Toxicity	Species	Product	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000*	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000*	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>1080 and ≤ 1960#	Moderate to high toxicity
Skin irritation	Rabbit	Non-irritant*	
Eye irritation	Rabbit	Non-irritant#	
Skin sensitisation (Guinea Pig Maximisation Test)	Guinea Pig	Non-sensitiser*	

*Based on toxicological studies on the product.

#Based on toxicological studies on metofluthrin.

Absorption, distribution, metabolism, excretion

Metofluthrin (radiolabelled), following single oral doses of 1 or 20 mg/kg bw was well absorbed, with systemic absorption of approximately ~40-77% following bile duct cannulation in rats, and with a T_{max} of 3-7 hours. In distribution studies, nearly all of the metofluthrin was found in intestinal tract, or had been excreted, with the highest tissue concentrations in the liver and muscle (2-5% and 1-2% of applied dose respectively at 6 h). There was no evidence of bioaccumulation in any particular tissue even after repeat-dosing. Absorbed metofluthrin was nearly completely metabolised, with no particular metabolite dominating the profile. Some unchanged metofluthrin was detected in faeces, presumably representing unabsorbed compound. Following a single dose, metofluthrin was excreted in both urine (10-26%) and faeces (30-56%), with less than 1.4% of the dose excreted in the expired air. Following repeated administration (21 days), approximately 56.7-74.6% was excreted in urine and 21.7-38.3% in the faeces. The excretion of metofluthrin was rapid, and appeared to be limited by the absorption.

Repeat-dose toxicity

Metofluthrin was administered in the diet at doses of up to approximately 1000 mg/kg bw/d in rats, 590 mg/kg bw/d in mice, 250 mg/kg bw/d in rabbits (developmental study) and 100 mg/kg bw/d in dogs. Systemic effects noted in mice, rats, rabbits and dogs following exposure to metofluthrin were generally limited to decreased bodyweight and bodyweight gain, decreased food consumption, liver effects (rodents only), and neurological signs (discussed separately below in the section on neurotoxicity potential). In many cases, reductions in bodyweight were observed without any significant reductions in food consumption.

The lowest NOEL in repeat dose studies was 200 ppm in the 2-year rat study (equivalent to 8.24 and 10.12 mg/kg bw/d, in males and females respectively). Effects at the next highest dose of 900 ppm included liver effects (discussed below), reduced food consumption, bodyweight and bodyweight gain, and changes in haematology and biochemical parameters.

In repeat-dose toxicity studies by the oral route, the liver was identified as the target organ in rodents. Effects included increased liver weight, dark and enlarged livers, hepatocellular hypertrophy, increases in smooth endoplasmic reticulum and biochemical changes (increases in cholesterol, triglycerides, phospholipids, albumin and globulin).

Treatment related effects on haematology parameters were noted in male and female rats in the 104 week dietary study. These changes included increased red blood cells and prothrombin time and reduced mean corpuscular volume (MCV). The NOEL for this study was 200 ppm (8.24 and 10.12 mg/kg bw/d in males and females respectively), based on decreased food consumption, reduced bodyweight and bodyweight gain, changes in haematology and biochemical parameters and effects on the liver.

Mutagenicity

Metofluthrin was not mutagenic *in vitro*, with and without metabolic activation.

Genotoxicity

Metofluthrin was not genotoxic in *in vitro* or *in vivo* studies.

Neurotoxicity

Metofluthrin has similar neurotoxic effects to other pyrethroids. Clinical signs of toxicity observed in rats and dogs including tremor, vomiting (dogs only) and increased salivation (dogs only). In dogs, tremor was noted at 30 mg/kg bw/d and above. In rats, tremor was observed in maternal animals at 30 mg/kg bw/d in a rat developmental study. Vocalization and hyperactivity were also noted in a 90 day dermal study in rats at doses of 30 mg/kg bw/d and above.

In an acute oral neurotoxicity study in the rat, alterations in the FOB (landing foot splay) and motor activity were observed early after the treatment period at doses of 100 mg/kg bw/d. Histopathology of selected organs and tissues and specific locations of the central and peripheral nervous system revealed no treatment-related effects following both acute and repeated doses of metofluthrin.

Carcinogenicity

Liver tumours were observed in the 104-week combined chronic/oncogenicity study in rats at or exceeding the MTD. There was an increased incidence of hepatocellular adenoma and carcinoma in male rats at 38 mg/kg bw/d, and in hepatocellular adenomas and carcinomas in female rats at 47 and 96 mg/kg bw/d respectively. These tumours were associated with increased liver weight, hepatocellular hypertrophy and an increased incidence of clear cell foci, eosinophilic foci and mixed cell foci in the liver. Metofluthrin was not found to be carcinogenic in mice and was not mutagenic and/or genotoxic *in vitro* and *in vivo*.

However, it is considered that metofluthin induced liver tumours in the rat described above occur via a mode of action that is similar to phenobarbital and is not relevant to humans.

Reproduction and developmental toxicity

Metofluthrin is not a reproductive toxicant in rats, or a developmental toxicant in rats or rabbits.

Observation in humans

No information was provided.

Public exposure

The product is intended for domestic use as an insect repellent and is not intended to be used directly on food or food preparation areas or food utensils. The product is suitable for use in standard size rooms (4 x 4 m, approximately 2.1 g of metofluthrin). The product should be placed upright or hung in a desired spot near or around the house where air gently circulates such as entry points or near overhead fans. The product provides up to 28 days continuous protection, after which the whole device should be replaced.

Based on the expected use pattern of the product in domestic settings, the most likely route of exposure will occur when occupying areas where the product is in use. There is also the potential for accidental oral and dermal exposure in children from touching the product and from hand-to-mouth exposure after touching the product.

Domestic users may be directly exposed to the product when opening the packaging, hanging the product in the desired location, disposing of the used product and entering treated areas.

As mosquitoes persist in many area of Australia all year round, it is expected that the duration of product use would be long-term.

Dermal exposure was considered to be negligible due to the use pattern of the product and the low vapour pressure of the active constituent. Therefore the risk assessment was conducted for inhalational exposure only.

The daily systemic exposure was estimated to be 0.00216 mg/kg bw/d for adults and 0.0065 mg/kg bw/d for 1-2 year old children. The MOE values for adults and children aged 1-2 years were acceptable (i.e. MOE >100), therefore the OCS considers that there will be no undue risk to domestic users (adults or children) from use of the product.

International regulations

No information was provided.

Scheduling status

Metofluthrin is currently listed in Schedule 6.

Schedule 6

METOFLUTHRIN.

Scheduling history

Metofluthrin was first considered by the ACCS in February 2011. Toxicological evaluation of metofluthrin and risk assessment was carried out by the OCS (then OCSEH). OCSEH proposed that based on its toxicity profile of moderate acute inhalation toxicity and neurotoxicity (with clinical signs of neurotoxicity seen at 100 mg/kg bw in a rat acute neurotoxicity study, and at 30 mg/kg

bw/d in a 12-month oral study in dogs and in dams in an oral rat developmental study), it was appropriate to include metofluthrin in Schedule 6.

The ACCS recommended a new Schedule 6 entry be created for metofluthrin. The delegate concluded that the recommendations of the ACCS were clear and appropriately supported and decided to include metofluthrin in Schedule 6. The delegate also agreed that an implementation period of six months was appropriate.

In July 2014, the delegate referred a scheduling proposal to the ACCS to amend the current Schedule 6 to exclude mosquito repellent preparations containing 312 g/kg or less of metofluthrin from scheduling. The applicant indicated that the toxicity of the product (the substance impregnated onto non-woven polyester fabric, which is incorporated in a device that is designed to release the substance in the atmosphere) is the same as the toxicity of the substance. The committee recommended that based on the toxicity profile and use pattern/exposure to the product, the current Schedule 6 metofluthrin entry be amended to exempt impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk to Schedule 5. They agreed that the schedule 5 entry should specifically include the preparation and the refill.

The delegate accepted the advice tendered by the ACCS and agreed to include a new entry for metofluthrin in Schedule 5 and to amend the current Schedule 6 entry. While metofluthrin is a moderately toxic pyrethroid insecticide, the packaging and presentation of the product mitigates the exposure risk and warrants Schedule 5 inclusion. The implementation date for this decision was 1 February 2015.

Schedule 5 – New entry

METOFLUTHRIN in impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk.

Schedule 6 - Amendment

METOFLUTHRIN except when included in Schedule 5.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that the current Schedule 5 metofluthrin entry be amended:

METOFLUTHRIN,

- in impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk; or
- when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin for use as a mosquito repellent

The committee supported the implementation being as soon as possible.

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

The reasons for the recommendation comprised the following:

· Polyethylene slow release matrix mitigates risk

- Overall low toxicity, and risk of inhalation toxicity is low due to the formulation of the product

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts the advice of the ACCS and agrees to amend the current Schedule 5 entry for metofluthrin. While metofluthrin is a moderately toxic pyrethroid insecticide, the packaging and presentation of the product in a framed polymer matrix mitigates the exposure risk and warrants inclusion in Schedule 5.

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

The proposed implementation date is 1 October 2015. An early implementation date is proposed to facilitate marketing of the product when registered by the APVMA.

Schedule entry

Schedule 5 – Amendment

METOFLUTHRIN

- in impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk; or
- when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin for use as a mosquito repellent.

Public submissions on the interim decision

No public 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 reasons for the final decision are in keeping with those for the interim decision.

The delegate has confirmed the proposed implementation date of 1 October 2015

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[6] Australian Health Ministers' Advisory Council (AHMAC): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2015) [Scheduling Policy Framework]

Schedule entry

Schedule 5 – Amendment

METOFLUTHRIN

- in impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk; or
- when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin for use as a mosquito repellent.

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

2. Agriculture and Veterinary Chemicals

SUMMARY OF DELEGATE-ONLY FINAL DECISIONS

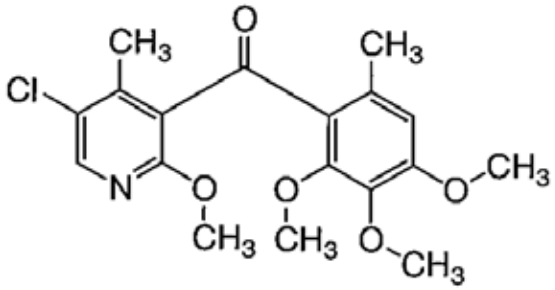
Substance	Final Decision
Pyriofenone	**Schedule 6 – amendment** PYRIOFENONE except when included in Schedule 5. **Schedule 5 – New Entry** PYRIOFENONE in preparations containing 30 per cent or less of pyriofenone Implementation date – 1 October 2015.
Dinotefuran	**Schedule 5 – New Entry** DINOTEFURAN Implementation date – 1 October 2015

2.1 PYRIOFENONE

Scheduling proposal

An application to the APVMA seeking registration of a product for agricultural uses requested that the delegate consider the scheduling of the active constituent, a suspension concentrate (SC) solution containing 300 g/L pyriofenone. In May 2015, the OCS, performed a risk assessment based on the information submitted to the APVMA

Substance summary



Structure of pyriofenone

Acute toxicity

Pyriofenone TGAC acute toxicity end-points are listed in the below table.

Toxicity	Species	Pyriofenone	SPF Classification
Acute oral toxicity LD50 (mg/kg bw)	Rat	>2000 (female, no deaths)	Schedule 5
Acute dermal toxicity LD50 (mg/kg bw)	Rat	>2000 (male and female no deaths)	Schedule 5
Acute inhalational toxicity LC50 (mg/m3/4h)	Rat	>5180 (male and female, no deaths)	Schedule 5
Skin irritation	Rabbit	Non-irritant	Not scheduled/ Appendix B
Eye irritation	Rabbit	Non-irritant	Not scheduled/ Appendix B
Skin sensitisation (maximization test)	Guinea pig	Sensitiser	Schedule 6

ISK Pyriofenone 300 SC Fungicide acute toxicity end-points are listed in the below table.

Toxicity	Species	ISK Pyriofenone 300 SC Fungicide	SPF Classification
Acute oral toxicity LD50 (mg/kg bw)	Rat	>2000 (male and female, no deaths)	Schedule 5

Acute dermal toxicity LD50 (mg/kg bw)	Rat	>2000 (male and female no deaths)	Schedule 5
Acute inhalational toxicity LC50 (mg/m^3/4h)	Rat	>2780** (male and female, no deaths)	Schedule 5
Skin irritation	Rabbit	Not a skin irritant	Not scheduled/ Appendix B
Eye irritation	Rabbit	Slight eye irritant	Schedule 5
Skin sensitisation (Buehler, 9 inductions)	Guinea pig	Not a skin sensitiser	Not scheduled/ Appendix B

**Maximum achievable concentration

Repeat-dose toxicity

A NOEL of 9 mg/kg bw/d was established for Pyriofenone based on a 1-year and a 2-year chronic rat study for signs of altered liver function, bilirubin and alkaline phosphatase decrease in males and increased kidney chronic nephropathy incidence in females at 42.9 and 46.5 mg/kg bw/d in males and females, respectively. Repeat dose toxicity studies' findings are compatible with Schedule 5.

Mutagenicity & Genotoxicity

Pyriofenone was not mutagenic in bacterial and mammalian cells and not clastogenic in mammalian cells, with and without metabolic activation. Pyriofenone did not induce micronuclei *in vivo* in mouse bone marrow following oral administration up to and including the limit dose of 2000 mg/kg bw. Therefore, from the available data, there is no evidence that pyriofenone is an *in vivo* genotoxicant.

Carcinogenicity

Pyriofenone was not carcinogenic in rats and mice.

Reproduction and developmental toxicity

Pyriofenone did not demonstrate evidence of reproductive/developmental toxicity potential. In rats, the NOEL for reproductive toxicity was 5000 ppm (equivalent to 339/485 mg/kg bw/d in males/females), the highest dose tested. The NOEL for offspring was 1000 ppm (equivalent to 65.2/92.3 mg/kg bw/d in male/female pups) based on lower absolute and relative splenic weights seen in F1 and F2 pups at 5000 ppm (equivalent to 339/485 mg/kg bw/d in male/female pups).

Observation in humans

No information was provided.

Public exposure

ISK Pyriofenone 300 SC Fungicide is for professional use only. No worker exposure studies or calculations of exposure have been submitted, but enough information was provided for the OCS to

carry out exposure estimations. The OCS concluded that acceptable margins of exposure (MOE) were expected without any personal protective equipment (PPE) when mixing/loading and spraying the product with airblast, ground boom or handwand. PPE were required to ensure acceptable MOE in the assessment when areas were sprayed with equipment carried on the back of the user. Finally, the OCS determined that potential harm caused by ISK Pyriofenone 300 SC Fungicide could be reduced through the use of appropriate packaging with simple warnings/precautionary statements and safety directions on the label, according to Schedule 5.

International regulations

The OCS found no evidence of pyriofenone based product being registered for use in any overseas jurisdiction. Pyriofenone active constituent and end-use product were submitted to the EU EFSA for approval in March 2010. Target crops were grapevines and wheat. An application for approval of an import tolerance (MRL) in grapevines, cucurbit vegetables; and berry & small fruit, has been submitted to the US EPA and is due in 2016. These applications in the EU and in the USA appear to remain pending.

Scheduling history

Based on an application for scheduling, the delegate made a delegate-only decision to include pyriofenone in Schedule 6. This decision was published on 28 October 2014.

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*;
- SPF scheduling factors[7];
- Other relevant information.

Delegate's final decision

Pyriofenone, a fungicide in the aryl phenyl ketone chemical family. While its overall toxicological is consistent with SPF criteria for listing in Schedule 5, evidence of sensitising potential resulted in it being listed in Schedule 6 (in February 2015). The current application seeks re-scheduling of a suspension concentrate product containing 30% of the active ingredient. The OCS report notes that testing of this product in the Guinea Pig maximisation test for sensitisation showed no evidence of sensitisation. The delegate therefore accepts the advice of the OCS to make an exception to the Schedule 6 entry allowing for listing of this product in Schedule 5. The delegate notes that the applicant has not objected to the OCS scheduling proposal.

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

Schedule Entry

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[7] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [Scheduling Policy Framework]

Schedule 6 - amendment

PYRIOFENONE **except** when included in Schedule 5.

Schedule 5 – New Entry

PYRIOFENONE in preparations containing 30 per cent or less of pyriofenone

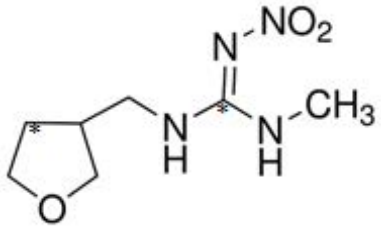
2.2 DINOTEFURAN

Scheduling proposal

In April 2015, the OCS, based on an application made to the APVMA to approve a new active ingredient, requested that the delegate consider creating a new entry for dinotefuran in Schedule 5 of the SUSMP. The reasons for the request were:

- An applicant submitted a data package to the APVMA seeking approval of the new active ingredient dinotefuran, a member of the neonicotinoid class of chemical. As a new chemical for AgVet use, it will require consideration by the delegate for scheduling prior to final registration of products containing this active constituent.
- Currently proposed products attached to this application are for agricultural use. However, in pre-submission meetings with the active ingredient applicant, it has been foreshadowed that veterinary chemical products (e.g. spot-on flea treatments) containing dinotefuran are also proposed for registration in the future.

Substance summary



Structure of dinotefuran. The position of the ^{14}C radiolabels used in ADME studies are indicated by an asterisk *

Acute toxicity

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

Toxicity	**Species**	**Dinotefuran**	**SPF Classification**
Acute oral toxicity LD50 (mg/kg bw)	SD Rat CD-1 Mouse	2450 2371	Schedule 5
Acute dermal toxicity LD50 (mg/kg bw)	SD Rat	>2000 (no deaths)	Schedule 5
Acute inhalational toxicity LC50 (mg/m3/4h)	Wistar Rat	>4090 (no deaths)	Schedule 5

Skin irritation	NZW rabbit	Non-irritant	
Eye irritation	NZW rabbit	Moderate irritant (OCS classification) Not classified as eye irritant by NOHSC Approved Criteria	
Skin sensitisation (GPMT method)	BR Guinea pigs	Not sensitising	

Repeat-dose toxicity

Short-term and subchronic toxicity studies in rats, mice and dogs reported decreases in body weight and decreased body weight gain as the main treatment-related effects. These effects were observed at generally high doses in rodents, and at lower doses in dogs. It should be noted that no NOEL could be established in the 13 week dog dietary study for females due to reduced body weight and body weight gains in all treatment groups. A short-term dermal toxicity study in rats did not elicit similar responses to those seen in the oral studies, with only skin-specific effects seen in rats treated with 1000 mg/kg bw/d. A short-term inhalational study in rats elicited similar responses to those seen in the oral studies at all treatment levels in females. Long term studies in rats, mice and dogs were consistent with the observations noted in shorter duration repeat dose studies.

Mutagenicity/Genotoxicity

There was no evidence of mutagenic and genotoxic potential *in vitro*, or a genotoxic potential *in vivo*.

Carcinogenicity

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

Reproduction and developmental toxicity

Dinotefuran was not a reproductive toxicant in rats. Effects were restricted to reduced body weight and body weight gain in parental and neonates of both generations. Dinotefuran was not a developmental toxicant in rats or rabbits, with effects restricted to reduced body weight and body weight gain in parental animals. No foetal effects were seen.

Other toxicology endpoints

Dinotefuran was found to not be acutely neurotoxic at relatively high doses (1500 mg/kg bw) with neuropathology negative up to the highest dose tested. Other than reduced body weight and body weight gains at high doses (3413 mg/kg bw/d) no effects were seen to indicate neurotoxicity in a 13 week dietary study. Dinotefuran was not a developmental neurotoxicant in rats at levels that induced maternal toxicity.

In guideline-compliant immunotoxicity studies in mice and rats, no effects were seen from treatment with dinotefuran. Dinotefuran is not considered to pose any immunotoxicity risk.

Observation in humans

No information was provided.

Public exposure

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

As indicated above, the applicant has foreshadowed that veterinary chemical products (e.g. spot-on flea treatments) are in development—these veterinary products have been approved in other jurisdictions such as Europe.

International regulations

Dinotefuran has been approved for use by the US EPA for agricultural use and by EMA for veterinary spot-on use European Medicines Agency.

JMPR has also evaluated the toxicology of dinotefuran previously.

Scheduling history

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

According to the Poisons Standard (2015), a number of chemicals in this class (neonicotinoids) have been previously scheduled; imidacloprid, acetamiprid, clothianidin, thiacloprid and thiamethoxam are listed in Schedule 6. Exemptions to Schedule 5 were noted for the following chemicals:

- imidacloprid in preparations containing 20 percent or less;
- clothianidin in preparations containing 20 percent or less; and
- thiamethoxam in preparations containing 60 percent or less,

There are additional exemptions (to not requiring scheduling) for the following chemicals:

- acetamiprid in preparations containing 1 percent or less; and
- imidacloprid in preparations containing 5 percent or less.

Delegate Considerations:

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- OCS evaluation report;
- Section 52E of the *Therapeutic Goods Act 1989*;
- SPF scheduling factors[8];
- Other relevant information.

[8] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [Scheduling Policy Framework]

Delegate's final decision

Dinotefuran is an insecticide in the neonicotinoid class. While other members of this class have a primary listing in Schedule 6 (with some product exemptions to Schedule 5), the toxicological profile of dinotefuran is clearly consistent with SPF guidance for inclusion in Schedule 5. Evidence of mild/moderate skin/eye irritancy for the formulated product means that is inappropriate to provide a schedule exemption for the formulated product considered in the application.

The delegate confirmed the implementation date of 1 October 2015.

Schedule entry

Schedule 5 – New Entry

DINOTEFURAN