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

October 2014

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 2014 joint meeting of the ACCS and the ACMS (joint ACCS-ACMS 8);
- scheduling proposals initially referred to the July 2014 joint meeting of the ACCS and the ACMS (joint ACCS-ACMS 9); and
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published for the March joint meeting on 30 January 2014 at: http://www.tga.gov.au/newsroom/consult-scheduling-accs-1403.htm and for the July joint meeting on 29 May 2014 at: http://www.tga.gov.au/newsroom/consult-scheduling-accs-1407.htm.

No public submissions were received for the March joint meeting. Edited versions of the public submissions received for the July joint meeting in response to this invitation were published on 30 September 2014 at: http://www.tga.gov.au/industry/scheduling-submissions-accms-1407.htm.

Interim decisions

The delegates' interim decisions on recommendations by the joint ACCS-ACMS 8 and 9 were published for the March meeting on 27 June 2014 at: http://www.tga.gov.au/industry/scheduling-decisions-1406-interim.htm and for the July meeting on 30 September 2014 at:

http://www.tga.gov.au/industry/scheduling-decisions-accms-1409-interim.htm. 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 these public submissions received in response to this invitation are published at: http://www.tga.gov.au/industry/scheduling-submissions.htm.

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 http:www.tga.gov.au/industry/scheduling-spf.htm.

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 http:www.tga.gov.au/industry/scheduling-poisons-standard.htm.

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

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

Abbreviation	Name
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name
ISO	International Standards Organization
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme

Abbreviation	Name
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])
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

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

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

1. Scheduling proposals referred to the March 2014 joint meeting of the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling (ACCS-ACMS 8)

1.1 LAURYL SULFATES

Scheduling proposal

On December 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme, requested the delegate consider amending the current Schedule 6 and Appendix E sodium lauryl sulfate entries to include ammonium lauryl sulphate and potassium lauryl sulfate.

The delegates' reasons for referring this proposal to the joint meeting of the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) include:

- The scheduling of sodium lauryl sulfate was last considered at the February 2010 and June 2010 meetings of the National Drugs and Poisons Scheduling Committee (NDPSC), and finalised at a joint meeting of the ACCS and ACMS in December 2010. The current proposal, referred *via* a NICNAS IMAP report, is to broaden the current entry so that it captures the potassium and ammonium salts.

- If the joint committee of ACCS-ACMS (ACCS-ACMS) considers that the current scheduling of sodium lauryl sulfate remains appropriate, the simplest amendment might be to delete the words *(excluding its salts or derivatives)* from the current Schedule 6 entry. If so, should current citations of the specific sodium salt also be deleted from the wording and should the entry be generalised to LAURYL SULFURIC ACID and its salts?

- Alternatively, the ACCS-ACMS might recommend that separate, parallel entries be developed for the two specified salts. If this is the proposed solution, are all the current sub-clauses and cut-offs appropriate?

- At the June 2010 NDPSC meeting, it was noted that preparations containing other salts of lauryl sulfate could be scheduled inadvertently, unless the words *(excluding its salts or derivatives)* were included in the Schedule 6 entry. The ACCS-ACMS may want to consider this in relation to the proposed broadening on the current entry to include the potassium and ammonium salts, as specified in the NICNAS IMAP report. Are the use patterns and toxicological profiles of the potassium and ammonium salts sufficiently similar to the sodium salt to warrant comparable sub-clauses? Are there likely to be different types of products on the market containing the ammonium and potassium salts that would now be scheduled?

- Are the current Appendix E statements for sodium lauryl sulfate (there is no Appendix F entry) appropriate for the potassium and ammonium salts, or should new entries be developed?

- Is the ACCS-ACMS able to offer any advice on whether the packaging issue (potential for children to ingest bright coloured liquid laundry detergent capsules) is an issue that requires scheduling consideration?

Substance details

Please refer to the NICNAS IMAP human health tier II assessment report for sodium, ammonium and potassium lauryl sulfate. This report is available on from the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=184.

Scheduling status

Sodium lauryl sulfate (SLS) is listed in Schedule 6 and Appendix E.

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

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

IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

(b) in leave-on preparations containing 1.5 per cent or less of sodium lauryl sulfate;

(c) in toothpaste and oral hygiene preparations containing 5 per cent or less of sodium lauryl sulfate;

(d) in other preparations for animal use containing 2 per cent or less; or

(e) in other preparations containing 30 per cent or less of sodium lauryl sulfate and, if containing more than 5 per cent sodium lauryl sulfate, 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

Poison	Standard Statement
Sodium lauryl sulfate	
• 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

SLS was first considered by the NDPSC in February 2010. This consideration was based on an Office of Chemical Safety (OCS, then 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 SUSMP.

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".

Public pre-meeting submissions

Two pre-meeting public submissions were received.

The first submission supported the principle of broadening the sodium lauryl sulfate (SLS) entry to include ammonium lauryl sulfate (ALS) and potassium lauryl sulfate (PLS), noting that all 3 substances have similar properties. However, the submission stated for the extension of the entry to include ALS and PLS, all 3 salts must have the same hazard or risk characterisation. The submission noted that the IMAP report stated the substances had similar but not identical properties. The submission also provided information regarding ALS and SLS being on the TGA Australian Register of Therapeutic Goods (ARTG) ingredients list, with them being used in therapeutic washes, shampoos and other topical products. The submission raised concerns regarding the potential impact on products currently marketed and whether it was appropriate to apply the same cut-off levels in view of a lack of product formulation information. The submission asked the delegates to consider an appropriate transition period should the decision be made to widen the scope of the Schedule 6 entry to allow manufacturers and suppliers time to make the required changes.

The second submission noted that ALS and PLS have similar irritancy profile as that of SLS and that this was the basis to align the scheduling of the 3 salts. As most surfactants, like the lauryl sulfate salts, are likely to be eye irritants, the submission requested that the committee and the delegates consider removing SLS and other surfactants from the SUSMP as they are unconvinced that the scheduling of a surfactant based on its irritancy is warranted. Removing SLS and not scheduling ALS and PLS aligns with current practice in the European Union and the United States of America. If scheduling were to remain and include other surfactants, then the submissions asked to increase the exemption to 35 per cent for rinse-off products as currently available cosmetic products contain ALS concentrations between 30 and 35 per cent.

Summary of the ACCS-ACMS advice to the delegates

The committee recommended that ammonium lauryl sulfate and potassium lauryl sulfate do not require schedule listing with sodium lauryl sulfate as the information provided to the committee was not sufficient to warrant scheduling.

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

The reasons for the recommendation comprised the following:

- Information provided is not sufficient to warrant scheduling.

Delegates' interim decision

The delegates have considered the advice provided by the joint meeting of the ACCS-ACMS and the two public submissions considered at that meeting. The delegates have not accepted the advice of the ACCS-ACMS and instead have made an interim decision to amend the current Schedule 6 and Appendix E entries for sodium lauryl sulfate (SLS) to include other lauryl sulfate salts, as recommended in the NICNAS IMAP report. The NICNAS supplementary advice also emphasised the need to capture all salts of lauryl sulfate in the current entry. The delegates note that skin irritancy and the potential for severe eye damage have driven the current scheduling of SLS, and that current SLS scheduling is consistent with SPF criteria for Schedule 6 listing for the pure substances. The NICNAS IMAP report makes the case that other salts of dodecyl (lauryl) sulphate would have similar skin/eye irritancy potential, and it therefore makes sense to broaden the current SLS entries (that currently exclude salts and derivatives) to bring consistency to the scheduling of products that use any of the lauryl sulphate salts for their surfactant properties. The delegates note the points raised in industry submissions that the toxicity profile of most surfactants are comparable to the lauryl sulphate salts and that current cut-offs from Schedule 6 to exempt may capture some products not currently scheduled. Accordingly, the delegates propose an implementation date (1 June 2015) that should enable product re-labelling to occur in an orderly manner.

The intent of the proposed actions in this interim decision is to capture the ammonium and potassium salts in the current Schedule 6 entry for the sodium salt (SLS), with the same exemption cut-offs. This could be achieved by either deleting references to the sodium salt in the current Schedule 6 and Appendix E entries, or creating parallel entries for the ammonium and potassium salts (believed to be the only other salts currently used in products available in Australia). The

delegates have opted for the first approach, but including cross-references in the SUSMP index to SLS to alert product manufacturers to the schedule changes.

The delegates note an issue raised in an industry submission, that the irritancy potential of the ammonium and potassium salts may be less marked than that of SLS, and that some products have been marketed with up to 35 per cent of these salts without apparent public health harm. However, the delegates had insufficient information at this time to justify modification of the exemption concentrations in the current SLS entry.

The delegates agree with the implementation date being 1 June 2015.

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

Public submissions on the interim decision

Two submissions were received. The first submission indicated that it supports the delegates' interim decision to amend the current sodium lauryl sulfate entry to include all lauryl sulfate salts. By making the entry specific to lauryl sulfate salts, lauryl sulfate derivatives are still exempt from scheduling, considering ingredients such as sodium laureth sulfate are commonly used as a safer alternative to SLS in cosmetic products.

The second submission noted that as there are no regulatory restrictions placed on any of these surfactants anywhere else in the world, including sodium lauryl sulfate, and noting that mild to moderate skin and eye irritancy of surfactants is well known by the general public, these surfactants should be unscheduled. This would remove the current need for some imported rinse-off cosmetic products to be over-labelled with the Appendix E statement.

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

Delegates' consideration

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS-ACMS advice;
- Supplementary advice from NICNAS;
- Section 52E of the Therapeutic Goods Act 1989;
- Scheduling factors[1]; and
- Other relevant information.

[1] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Delegates' final decision

The delegates note the points made in public submissions relating to the pre-meeting consideration and the interim decision. Noting that the joint meeting of the ACCS and ACMS did not support overturning previous scheduling recommendations and decisions to remove the current schedule 6 entry for sodium lauryl sulphate, the delegates confirm their intent to simply broaden the entry to include other salts of lauryl sulphate. The delegates note that this action is supported in the public submission. However, the submissions note that removing reference to 'derivatives' in the entry potentially broadens the scope of the intended change. This was not the intent, nor the advice of the joint ACCS-ACMS meeting. Accordingly, the delegates have decided to **vary** the interim decision, and to restore the exclusion of 'derivatives' to the schedule entry. While there is a separate and closely parallel entry in Schedule 6 for LAURETH CARBOXYLIC ACIDS, restoration of the words 'excluding its derivatives' in the modified LAURYL SULFATE SALTS entry would allow for the continued exemption from scheduling for **sodium laureth sulfate** at the present time.

The delegates confirm the implementation date of 1 October 2015 to allow for product re-labelling to occur in an orderly manner.

Schedule entry

Schedule 6 – amend entry as follows:

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

(a) 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;

(b) in leave-on preparations containing 1.5 per cent or less of ~~sodium~~ lauryl sulfates;

(c) in toothpaste and oral hygiene preparations containing 5 per cent or less of ~~sodium~~ lauryl sulfates;

(d) in other preparations for animal use containing 2 per cent or less; or

(e) 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
~~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.

INDEX – New entry

SODIUM LAURYL SULPHATE

See LAURYL SULFATE SALTS

DODECYL SULFATES

See LAURYL SULFATE SALTS

2. Scheduling proposals referred to the July 2014 joint meeting of the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling (ACCS-ACMS 9)

2.1 3,7-DIMETHYL-2,6-OCTADIENAL ISOMERS (CITRAL, GERANIAL AND NERAL)

Scheduling proposal

The joint committee of the ACCS-ACMS considered the following proposal referred by the chemicals scheduling delegate and the medicines scheduling delegate (the delegates) for advice:

- Proposal for a new Schedule 5 entry with a yet to be determined low concentration cut-off level.

The committee also considered and discussed the resolutions with an implementation date of 1 February/1 July/1 October 2015.

The application relating to three isomers of 3,7-dimethyl-2,6-Octadienal (citral, geranial and neral) is one of several chemicals referred by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) following assessment under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme.

The delegates' reasons for referring this scheduling proposal to the joint meeting of the ACCS-ACMS are that the primary public exposure to citral compounds is likely to be *via* use of cosmetics, fragrances and other domestic products (polishes, paints, washing and cleaning products, finger paints and modelling clay), with other possible uses as a component of pest control products, flavourings and disinfectants, and possibly as fragrance ingredients of therapeutic goods.

The matter was first considered by the ACCS at the November 2013 meeting. The ACCS advised the delegate that the three substances should be included in Schedule 5, but that a cut-off to exempt from scheduling could not be determined. The ACCS advised that further information be sought on the extent of use and/or presence of these substances in fragrances in Australian products in order to assess the potential regulatory impact of setting an exemption cut-off level. The ACCS also pointed to the potential for these substances to be components of essential oils, some of which would have different existing schedule entries (e.g. geranium oil is currently exempt from scheduling *via* listing in Appendix B).

The delegates sought further information from industry in relation to these matters and sought further advice from the joint committee of the ACCS-ACMS on how best to manage the scheduling aspects of this submission. The advice from the joint meeting of the ACCS-ACMS was sought on the basis that, while the industry-provided information relates mainly to uses in cosmetics, fragrances and household cleaners, some therapeutic goods may include these substances as excipients.

The delegates asked the following specific questions to the ACCS-ACMS:

- The relatively low toxicity profile of these chemicals suggests consistency with the *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) criteria for Schedule 5. However, public exposure is only likely to occur through the use of products with concentrations ranging up to 5%, at which concentration adverse health effects are unlikely. Does the joint committee of the ACCS-ACMS consider that listing in the SUSMP is appropriate? If so, should they be listed in Schedule 5, with an appropriate cut-off to exempt (5%?)?

- If scheduled, what name should be used in the listing (e.g. 3,7-dimethy-2,6-Octadienal, with indexing cross-references to the three isomers of citral, geranial and neral)?

- Some of these isomers are known to be components of various essential oils. If the three isomers are listed in Schedule 5, is there a potential ambiguity with the current listing of geranium oil and lemongrass oil in Appendix B or any other schedule entries for essential oils, including those not specifically scheduled?

- There are quite low concentration limits (0.001% and 0.01%) in EU Cosmetic Directive 76/768/EEC Annex III Part 1 specifying the highest concentrations permitted in cosmetic and personal care products without labelling. Is it feasible to include these limits in any scheduling proposal?

- Is it feasible to include concentration limits in other types of products in the schedules, based on the calculations in the dermal sensitisation Quantitative Risk Assessment (QRA) of the International Fragrance Association (IFRA), as reported in the NICNAS IMAP report?

- Does the information provided by industry assist the ACCS-ACMS to recommend a suitable cut-off level for a Schedule 5 entry? Should any Schedule 5 entry be specific for cosmetic/cleaning products to limit any regulatory impacts on other types of products?

- How does the ACCS-ACMS advise on a schedule entry that could potentially exclude the presence of any of the three isomers in essential oils - note that the highest concentrations in

some Schedule 5 or unscheduled essential oils can be in the 20-40% range, or even 80% citral in the case of lemongrass oil (currently listed in Appendix B)? Is there a case for a proposed Schedule 5 listing to specifically exempt the three isomers when added or present as a component of an essential oil?

Substance summary

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

Scheduling status

3,7-Dimethyl-2,6-octadienal isomers are not specifically scheduled.

Scheduling history

3,7-Dimethyl-2,6-octadienal isomers are not currently listed in the schedules, although there was some initial consideration of possible listing in Schedule 5 at the November 2013 ACCS meeting.

Pre-meeting public submissions

Two submissions were received. The first submission indicated that if scheduling is required for these substances, a low concentration exemption cut-off in line with the International Fragrance (IFRA) Standards may be appropriate.

The second submission indicated that the substance should remain unscheduled. If, however, a schedule listing is required, cosmetic preparations containing the substance should be exempted from scheduling.

The public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Summary of ACCS-ACMS advice to the delegate

The joint committee of the ACCS-ACMS recommended that cosmetic and household cleaning preparations containing more than 5% of citral be listed in Schedule 5.

The ACCS-ACMS recommended an implementation date of 1 February 2015.

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

The reasons for the recommendation comprised the following:

- Due to extensive use of these substances in products available in Australia, there is a risk for excessive repeated exposure.
- Risk of skin irritation and sensitisation at concentrations greater than 5%.

- Toxicity profile is consistent with the scheduling factors for Schedule 5.
- Use in cosmetics coming into contact with skin.

Delegates' interim decision

The delegates accept the advice of the ACCS-ACMS that a new Schedule 5 entry be created for citral, based on a toxicological profile that is consistent with SPF criteria for listing in Schedule 5, specifically the potential to cause skin irritation and sensitisation. However, the delegates note that this would only capture one of the three isomers under consideration. While there are INCI names for two of the three isomers under consideration (citral and neral), the third isomer would need to be separately scheduled under its chemical name. The delegates consider that listing in schedule 5 under the name 3,7-Dimethyl-2,6-octadienal would capture all three isomers, and that cross-referencing the names citral, neral and geranial in the SUSMP index would facilitate industry understanding of the schedule listing. The delegates also accept ACCS-ACMS advice that the Schedule 5 listing be specific for cosmetic and household cleaning products, where the potential for skin sensitisation is most relevant. This avoids capturing therapeutic goods containing these substances, where the regulatory risk assessment can be applied on an individual product basis.

The delegates note the difficulties in determining an appropriate exemption cut-off for the proposed Schedule 5 entry, and accept the ACCS-ACMS advice that a 5% cut-off to exempt provides appropriate public health protection, while minimising regulatory impacts on industry associated with the widespread use of the three isomers as fragrance ingredients.

The delegates also note that some essential oils can contain varying amounts of 3,7-Dimethyl-2,6-octadienal isomers, and this could result in the inadvertent capture of essential oils containing more than the 5% cut-off. The advice from the ACCS-ACMS indicated that the proposed Schedule 5 listing could impact on two currently exempted essential oils listed in Appendix B, geranium oil and lemongrass oil. The proposed Schedule 5 listing may not be a problem for geranium oil, where the geranial component would only exceed 5% when a substantial amount of the geraniol content (up to 25%) is converted to geranial by autoxidation. Unlike geranial, geraniol is not considered to be a potential sensitiser. On the other hand, lemongrass oil, containing up to 90% citral, would be captured by the proposed Schedule 5 listing. The delegates therefore propose to foreshadow the removal of lemongrass oil from Appendix B, to list it in Schedule 5 with a 5% cut-off, and to seek industry comment on any regulatory implications.

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

The preferred listing (see notes above) is:

- 3,7-DIMETHYL-2-6,-OCTADIENAL and its isomers, in cosmetic and household cleaning preparations **except** in preparations containing 5 per cent or less of 3,7-Dimethyl-2,6-octadienal isomers.

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS-ACMS advice;
- Section 52E of the Therapeutic Goods Act 1989;
- Scheduling factors[2];
- Other relevant information.

Public submissions on the interim decision

One submission was received, which was in support of the delegates' interim decision.

Delegates' final decision

The delegates note the submission received in response to publication of the interim decision and **confirm** the interim decision as no evidence has been received to alter the interim decision.

The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

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

A longer implementation period may be needed to allow for orderly re-labelling of any products affected by the scheduling decision. The delegates propose an implementation date of 1 June 2015.

Schedule entry

Schedule 5 – New entry

3,7-DIMETHYL-2-6,-OCTADIENAL and its isomers in cosmetic and household cleaning preparations **except** in preparations containing 5 per cent or less of 3,7-DIMETHYL-2-6,-OCTADIENAL isomers.

SUSMP Index – New entries

Citral – see 3,7-Dimethyl-2,6-octadienal

Neral – see 3,7-Dimethyl-2,6-octadienal

Geranial – see 3,7-Dimethyl-2,6-octadienal

[2] National Coordinating Committee on Therapeutic Goods (NCCTG): Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

2.2 TRIETHANOLAMINE

Scheduling proposal

The joint committee of the ACCS-ACMS considered the following proposal referred by the chemicals scheduling delegate and the medicines scheduling delegate (the delegates) for advice:

- Proposal to include an entry for triethanolamine in Schedule 4 (or Appendix C) to address the potential use of this chemical in preparations for tattoo removal.

The committee considered and discussed the resolutions with an implementation date of either 1 February/1 June/1 October 2015.

The delegates' reasons for referring this scheduling proposal to the joint meeting of the ACCS-ACMS was that, in accordance with section 4.2 of the *Scheduling Policy Framework for Medicines and Chemicals*[3] (SPF, 2010), advice is required to be obtained from an expert advisory committee for all rescheduling proposals.

The risk assessment report for triethanolamine was prepared by the National Industrial Chemical Notification and Assessment Scheme (NICNAS) under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme and is a publicly available document containing sufficient information for the ACCS-ACMS to provide advice. Furthermore, its recommendations would be known to industry.

The NICNAS IMAP report draws specific attention to the risks of using triethanolamine in preparations injected intra-dermally to assist with the removal of tattoos. Advice of the joint committee of the ACCS-ACMS is needed as to whether this specific use requires control *via* listing triethanolamine preparations for such use in Schedule 4 (or Appendix C).

The delegates sought the following specific advice from the ACCS-ACMS:

- What scheduling actions could best give effect to the NICNAS recommendation to restrict the use of triethanolamine applied intra-dermally for tattoo removal? Would this be a specific listing in Appendix C, or a new entry in Schedule 4 (similar to that for ethanolamine)?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *ethanol, 2,2',2''-nitrilotris-*. This report is available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=427.

Scheduling status

This chemical (excluding its salts and derivatives, except in preparations containing 5% or less of triethanolamine) is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 5.

[3] National Coordinating Committee on Therapeutic Goods (NCCTG): Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Schedule 5 chemicals are labelled with 'Caution'. These are substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

This chemical is included in Appendix E with the standard statements of G3 'If swallowed, do NOT induce vomiting', 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'; and in Appendix E with a warning statement 'Irritant' and safety directions of 'Avoid contact with eyes' and 'Avoid contact with skin'.

Scheduling history

The toxicological information relating to triethanolamine (TEA), diethanolamine (DEA) and monethanoloamine (MEA) were considered by the NDPSC over several meetings in 1995, 1996 and 2000. Issues raised in the NICNAS IMAP report relating to the use of TEA in cosmetics and domestic products were considered at the November 2014 meeting of the ACCS. At that time, the delegate, acting on the advice of the ACCS, determined that the current listing of TEA in Schedule 5 remains appropriate. However, the delegate noted the advice of the ACCS that the issue of appropriate scheduling to limit the use of TEA in preparations for removal of tattoos should be referred to a joint meeting of the ACCS and ACMS for advice.

Pre-meeting public submissions

One submission was received and the submission suggested that any consideration of triethanolamine should be restricted to the intradermal use in tattoo removal preparations, noting that other uses of triethanolamine had been considered previously.

The public submission is available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Summary of ACCS-ACMS advice to the delegate

The joint committee of the ACCS-ACMS recommended that triethanolamine be included in Schedule 4 when in preparations for tattoo removal.

The ACCS-ACMS recommended an implementation date of 1 February 2015.

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.

The reasons for the recommendation comprised the following:

- Evidence of significant adverse health effects when used in tattoo removal. This use potentially requires medical supervision.

Delegates' interim decision

The delegates accept the advice of the ACCS-ACMS that triethanolamine be listed in Schedule 4 in preparations used to aid tattoo removal in humans. The delegates noted concerns raised about the potential for adverse effects associated with the use of chemical products containing triethanolamine in tattoo removal due to the irritant nature of such products, especially when injected intradermally. Tissue reddening, inflammation and possibly subsequent infection are likely

consequences of using the substance as a tattoo removal agent, where the removal of the pigments is dependent upon the inflammatory response. The delegates noted that laser removal is a medically-regulated procedure for tattoo removal and medical supervision *via* listing in Schedule 4 could ensure safer use of tattoo-removal preparations containing triethanolamine. Furthermore, the delegates agreed with the ACCS-ACMS that listing in Schedule 4 is a better option than attempting to restrict such products through listing in Appendix C.

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

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

One submission was received, which was in support of the Delegates' interim decision.

Delegates' final decision

The delegates note the submission received in response to publication of the interim decision and **confirm** the interim decision as no evidence has been received to alter the interim decision.

The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

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

The implementation date is 1 February 2015. An early implementation date is considered appropriate.

[4] National Coordinating Committee on Therapeutic Goods (NCCTG): Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Schedule entry

Schedule 4 – New entry

TRIETHANOLAMINE when in preparations for tattoo removal.

2.3 ZINC LACTATE

Scheduling proposal

The joint committee of the ACCS-ACMS considered the following proposal referred by the chemicals and medicines scheduling delegate (the delegates) for advice:

- Proposal for new a Schedule 6 entry for zinc lactate except in toothpastes containing 2.5 per cent or less of zinc lactate.

The committee considered and discussed the resolutions with an implementation date of either 1 February/1 June/1 October 2015.

Zinc lactate is a chemical referred by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) following assessment as a new chemical.

The delegates' reasons for referring this scheduling proposal to the joint committee of the ACCS-ACMS is that the proposed use of zinc lactate is as an ingredient of toothpastes, but other potential uses that could result in public exposure have not been identified. The NICNAS recommendation is that inclusion in Schedule 6 is warranted on the basis of its acute toxicity profile, particularly its irritancy potential, but that use in toothpastes at up to 2.5% should not produce adverse health effects in persons aged 12 years or older. The NICNAS new chemical assessment public report notes that this conclusion also applies to chronic exposure to absorbed zinc from the use of toothpastes. Advice from the joint committee of the ACCS-ACMS is needed on whether it is necessary to use scheduling to limit the use and concentration of this chemical in toothpastes and, if so, what is an appropriate schedule entry.

The delegates asked the following specific questions from the ACCS-ACMS:

- Does the ACCS-ACMS support inclusion of zinc lactate in Schedule 6, based on its acute toxicity profile, including its irritancy potential, with a cut-off to exempt at 2.5% when an ingredient of toothpastes?

- During consultation on the proposed scheduling action, including a submission relating to the interim decision, apparent inconsistencies were raised relating to the estimates on zinc exposure associated with the use of toothpastes containing 2.5% zinc lactate. The NICNAS assessment report indicated a potential oral intake of 0.0029 Zn^{++} mg/kg/d, which is approximately 0.174 mg/d for a 60 kg adult. An industry-related submission on the delegate's interim decision (for the November 2013 ACCS meeting, which was published on 27 February 2014) estimated the maximum daily zinc exposure to be 18.7 mg/d (assuming 100% bioavailability). This was reduced to approximately 1 mg Zn^{++}/d after accounting for dilution and rinsing associated with toothpaste use. Both these intake estimates, while markedly discrepant, appear to be within the Food Standards Australia New Zealand (FSANZ) recommended dietary intake (RDI) values of 12 mg/d for adults and 4.5 mg/d for children and provide an adequate Margin of Exposure

(MOE), if compared to the no observed adverse effect level (NOAEL) of 50 mg Zn^{++}/d used in the NICNAS assessment.

- The zinc intake estimates are also well below the 25 mg/d dose recommendation for medicines exempted from listing in Schedule 4 of the SUSMP.
- The delegate subsequently withdrew the interim decision of February 2014 to list toothpaste preparations containing zinc lactate in Schedule 6 except when 2.5% or less, and determined to seek further advice from a joint meeting of the ACCS-ACMS to resolve the question of whether the proposed 2.5% exemption is consistent with the Zn intake and MOE estimates.
- If there is justification for preventing the use of toothpastes containing zinc lactate in children less than 12 years of age, what specific scheduling and/or 'reverse scheduling' label statements are required?

Substance summary

Please refer to the NICNAS assessment report for zinc, bis[(2S)-2-(hydroxyl-.kappa.O)propanato-.kappa.O]-, (T-4)- (Zinc lactate). This report (STD/1388) is available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/new-chemical-assessments.

Scheduling status

Zinc lactate is not currently scheduled. A Schedule 4 entry exists for Zinc compounds for human internal use; however, as the use for this substance is not for human internal use, this entry is not applicable.

Scheduling history

Zinc lactate is not currently listed in the schedules, although there was some initial consideration of possible listing in Schedule 6 at the November 2013 ACCS meeting.

Pre-meeting public submissions

One submission was received. The submission requested that toothpastes containing zinc lactate when labelled with "not recommended for children under 12 years of age" be exempted from scheduling.

The public submission is available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Summary of ACCS-ACMS advice to the delegate

The joint committee of the ACCS-ACMS recommended that toothpaste preparations containing more than 2.5% zinc lactate be included in Schedule 6.

The committee, in addition to recommending a Schedule 6 entry, also recommended an Appendix F statement, namely "Not recommended for children under twelve years of age" for toothpaste containing zinc lactate.

The ACCS-ACMS recommended an implementation date of 1 February 2015.

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.

The reasons for the recommendation comprised the following:

- Potential risk of ingestion of excessive amounts of zinc in toothpaste, especially in children under 12 years of age.

Delegates' interim decision

The delegates note that the ACCS-ACMS has essentially confirmed the advice given by the ACCS at its November 2013 meeting, that the use of zinc lactate in toothpaste preparations be limited to 2.5% by listing toothpastes containing more than 2.5% zinc lactate in Schedule 6. The delegates further note that the ACCS-ACMS has confirmed the need to restrict the use of zinc lactate in toothpastes used by children under 12, by including a requirement for a label warning statement (*'not recommended for children under twelve years of age'*.) for both Schedule 6 products, *via* a new Appendix F warning statement, and for exempt products, *via* a 'reverse scheduling' statement in the Schedule 6 exemption clause.

The delegates note that the primary purpose behind the recommendation in the NICNAS report on zinc lactate, and the subsequent advice from the ACCS and ACCS-ACMS, was to restrict the concentration in toothpastes to 2.5% based on risk assessment calculations of daily zinc systemic intake. The Schedule 6 proposal is also partly based on the imprecise estimate of the acute lethal dose of zinc lactate, and an uncertain characterisation of its eye irritancy potential.

The delegates accept the ACCS-ACMS advice, noting that the TGA has approved zinc lactate (anhydrous and dihydrate) for use as a dental excipient in registered and listed toothpaste products, at a maximum concentration of 2.5%, for use only by adults and children aged 12 years and older.

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

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

[5] National Coordinating Committee on Therapeutic Goods (NCCTG): Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Public submissions on the interim decision

One public submission was received. This submission indicated that the proposed concentration cut-off for toothpaste preparations containing 2.5% or less of zinc lactate was lower than the US National Institute of Health (NIH) reported Tolerable Upper Intake Level for Zinc (Table 3 in the public submission). Therefore the more appropriate cut-off level to exempt zinc lactate from scheduling is 3%. Additionally, given that young children use smaller amounts of toothpaste with special care taken with toothpaste containing fluoride, it is expected that children get exposure to half of the adult exposure to toothpaste. Further, given the consideration of the tolerable upper intake level of zinc and the extremely conservative estimate of zinc exposure from toothpaste, the submitter believes that warning statements are unnecessary for toothpaste containing 3% or less zinc lactate. Consuming the entire quantity of toothpaste provides as much zinc as a single serving of some breakfast cereal.

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

Delegate's final decision

The delegates note the submission received in response to publication of the interim decision and **confirm** the interim decision.

The delegates note that the submission again raises the issue of disparities between the estimated amounts of systemic intake of zinc associated with the ingestion of toothpaste during use. The submission points out the estimated zinc intake would be below the Recommended Daily Intake (RDI), even for children under twelve years of age, and well below US NHI estimates of a tolerable upper limit for daily zinc intake, even if the proposed cut-off from Schedule 6 to exempt were to be lifted from the proposed 2.5% to 3%. The delegates agree that this appears to be a conservative assessment and to be inconsistent with the Margin of Exposure (MoE) estimates in the NICNAS report (59 for adults and lower for children).

Nevertheless, the delegates note that the proposed scheduling entries align with current restrictions on the concentration of zinc lactate in toothpaste (2.5%) and the recommendation that such toothpastes are not recommended for use by children under 12 years of age. This is the primary reason that the delegates have decided to confirm the interim decision.

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

The implementation date is 1 February 2016. This was the proposed implementation date published with the interim decision. It allows for an orderly process to re-label any products affected by the scheduling decision.

Schedule entry

Schedule 6 – New entry

ZINC LACTATE in toothpaste **except** in toothpaste preparations containing 2.5 per cent or less of zinc lactate and labelled with the statement *'not recommended for children under twelve years of age'*.

Appendix F, Part 1 – New entry

107. Not recommended for children under twelve years of age.

Appendix F, Part 3 – New entry

Poison	Warning Statement	Standard Statement
Zinc lactate in toothpaste.	107. Not recommended for children under twelve years of age.	

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

3. Agriculture and Veterinary Chemicals

3.1 FLURALANER

Scheduling proposal

In August 2014, the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to register a new active ingredient and the approval of five different tablets that containing various concentrations of fluralaner, referred the following proposal to be considered by the delegate:

- A proposal to create a new Schedule 5 listing for oral divided preparations, each containing 1400 mg or less of fluralaner per dosage unit, for the treatment and prevention of flea infestations and control of ticks in dogs.

The reasons for the request are that fluralaner:

- has low oral toxicity in rats (LD_{50} >2000 mg/kg bw);
- has low dermal toxicity in rats (LD_{50} >2000 mg/kg bw);
- has no skin irritation or eye irritation in rabbits; and
- is not a skin sensitiser in guinea pigs.

The OCS evaluation report indicated that no acute inhalational toxicity study was submitted for fluralaner. While the acute inhalational toxicity is unknown due to the general lack of specific toxicological data on the active constituent and formulation excipients, the lack of an acute inhalational toxicity endpoint is not considered a significant data deficiency, and does not affect the risk assessment of the product, noting that the formulated product is in a chewable form and is not expected to generate fine material of inhalational concern in this case.

Scheduling status

Fluralaner is not specifically scheduled.

Fluralaner belongs to a chemical group called isoxazolines. Isoxazoline substances, such as isoxaflutole and afoxolaner, are a partially saturated analogue of isoxazoles. Isoxaflutole is currently in Schedule 5. Afoxolaner, a chemical with a comparable use pattern and toxicology profile to that of fluralaner, in oral divided preparations each containing 140 mg or less of afoxolaner per dosage unit for the treatment and prevention of flea infestations and control of ticks in dogs, is also listed in Schedule 5.

Scheduling history

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

The scheduling history of a similar substance, afoxolaner, is provided below.

In April 2014, the delegate made a delegate only decision to list afoxolaner in Schedule 5. This decision was based on its low acute toxicity profile. The delegate noted that more significant toxicity would be expected with repeated dosage, due to accumulation of active drug. The acute poisoning risk to humans (in particular children) is low, in part due to the proposed packaging of only six tablets in a blister pack.

Substance summary

Fluralaner is a new molecular entity of the isoxazoline class that has shown potent acaricidal and insecticidal activity through a dual mechanism of binding to neuronal γ-aminobutyric acid (GABA)- and glutamate-gated chloride channels in susceptible invertebrates. Fluralaner has high selectivity for arthropods and a very favourable safety profile in vertebrates including dogs[6]. It is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA receptor and glutamate-receptor). In molecular on-target studies on insect GABA receptors of flea and fly, fluralaner is not affected by dieldrin resistance[7].

[6] Fluralaner, a novel isoxazoline, prevents flea (*Ctenocephalides felis*) reproduction *in vitro* and in a simulated home environment. Heike Williams, David R Young, Tariq Qureshi, Hartmut Zoller, and Anja R Heckeroth. Parasit Vectors. 2014; 7: 275. Published online Jun 19, 2014. doi:10.1186/1756-3305-7-275. Available at http://europepmc.org/articles/pmc4067686.

[7] http://ec.europa.eu/health/documents/community-register/2014/20140211127740/anx_127740_en.pdf

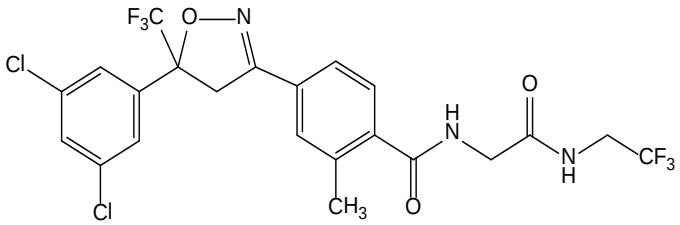

Figure 1. Structure of fluralaner

Acute toxicity

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

Toxicity	*Species*	*Fluralaner*	*SPF* Classification*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (no deaths)	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000 (no deaths)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to be assessed.
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Non-irritant	
Skin sensitisation (maximisation test)	Guinea pig	Non-sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010)

The OCS evaluation report indicated that no studies on the formulated product have been provided. Estimation of its acute toxicity suggests that the product is expected to have low acute oral and dermal toxicity. While acute inhalational toxicity is unknown, the formulation presentation of the product as a tablet is unlikely to result in acute inhalational toxicity risks. It is not expected to be a skin sensitiser, although it is expected to be a slight skin and eye irritant based on the formulation composition.

The acute toxicity end-points of all the constituents in the product are listed in the below table.

Toxicity	*Species*	*Preparations containing fluralaner*	*SPF* Classification*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	Not provided*	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	Not provided*	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Unknown (but likely to be low toxicity)**	Unable to be assessed.
Skin irritation	Rabbits	Slight-irritant*	
Eye irritation	Rabbits	Slight-irritant*	
Skin sensitisation (maximisation test)	Guinea pig	Not expected to be sensitising*	

* based on the toxicological profile of all constituents in the product.

** based on the formulation type as a chewable tablet.

Repeat-dose toxicity

In a number of short-term studies by both the oral and dermal route of exposure in rats, the main signs associated with treatment included minor variations in haematological and blood chemistry parameters, and organ weight changes. Of the organ weight changes, the liver was the most affected with increases in liver weights associated with fatty changes (diffuse and mid-zonal). The route of exposure did not markedly change the effects seen in treated animals, with similar haematological, blood chemistry and organ weight changes in both orally and dermally treated rats. Additional treatment-related findings in the oral toxicity study included thymic atrophy, zymogen depletion in the pancreas and diffuse vacuolation/hypertrophy in the adrenal cortices at high doses.

Mutagenicity

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

Genotoxicity

Fluralaner was not genotoxic in a standard suite of *in vitro* and *in vivo* genotoxicity studies.

Carcinogenicity

No carcinogenicity studies were submitted in support of fluralaner. The use pattern of the tablets as a quarterly treatment in a non-food-producing use situation, and noting the relatively minor effects

seen in short-term studies and the lack of any positive genotoxicity potential, the long-term toxicity potential associated with the proposed use of the active constituent as a veterinary medicine for companion animals (dogs) is likely to be low.

Reproductive and developmental toxicity

In a target animal (dog), no effects were seen in reproductive parameters (including litter viability and fecundity) at up to three times the proposed therapeutic dose. In developmental toxicity studies in the rat, minor effects were seen in treated foetuses, such as a slight decrease in foetal bodyweights, increases in dilated renal pelvis and ureter, and supernumerary ribs. The effects, however, were at dose levels where maternal effects (decreased food consumption and bodyweight gain) were observed, suggesting foetal effects were secondary to maternal toxicity. The OCS notes that developmental toxicity studies in a second species were not conducted, although on available evidence, fluralaner is not considered to be teratogenic or a developmental toxicant.

Observation in humans

No information provided.

Public exposure

It is expected that administration of tablets will primarily be conducted by members of the public, as pet owners, and veterinarians. Pet owners or members of the household may be exposed to the product when administering the tablet into the mouth of dogs(s) or *via* excreta (vomitus, urine/faeces).

Overall exposure to fluralaner during dosing is likely to be low. Administration of a chewable tablet formulation to non-food-producing companion animals is a low exposure pattern, with only dermal exposure likely to occur. The presentation as a chewable tablet with the majority of the tablet being excipients, with low levels of active constituent, is expected to result in low fluralaner exposure to the person administering the tablet.

While exposure during dosing is likely to be negligible, there is an increased likelihood of exposure to small amounts of fluralaner following dosing of domestic dogs, *via* contact with wet or partly macerated tablets, or when cleaning vomitus or urine/faeces (noting that dermal toxicity studies have identified that systemic exposure does occur with dermal contact with fluralaner). Emesis is not uncommon in dogs, while exposure to small amounts of fluralaner in faeces may occur during disposal.

Exposure routes will be primarily dermal with a limited possibility of subsequent hand-to-mouth or hand-to-eye exposure. Such exposure is likely to be minimal, as contamination of hands *via* emesis or excreta is likely to be obvious to an adult. As it is expected that dog owners will take normal hygiene measures such as washing hands after touching vomitus or coming into contact with faeces, it is likely that fluralaner will only be in contact with the skin for a short period of time, which will limit the amount absorbed through the skin and possible oral and ocular exposure. Potential oral and ocular exposure is considered to be minimal.

There is the possibility of an accidental exposure, where a child gains access to the product after removal from packaging and before administration to the dog. It is expected that such exposure

would be a single event, and may occur typically by the oral route, although dermal handling is also possible.

In a conservative worst-case scenario, where a 10 kg child gained access to a full package of very large tablets (4×1400 mg) and the product was consumed as an acute event, this would be equivalent to a total exposure of 560 mg/kg bw.

International regulations

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

In May 2014, the US Food and Drug Administration (US FDA) approved fluralaner with a condition that the products containing the substance may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to advise dog owners regarding use in breeding dogs, to monitor for and respond to adverse reactions, and to define the appropriate treatment interval (8 vs. 12 weeks) based on the species of ticks the dog is likely to encounter.

In December 2013, the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency recommended the granting of a marketing authorisation for the veterinary medicinal product Bravecto chewable tablets for dogs (112.5 mg, 250 mg, 500 mg, 1000 mg, 1400 mg) containing fluralaner.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- OCS evaluation report (not publicly available);
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[8];
- Other relevant information.

Delegate's final decision

Fluralaner belongs to a novel class of ectoparasiticides (isoxazoline-substituted benzamide derivatives), two other members of which have been listed in Schedule 5 (isoxaflutole and afoxolaner). The toxicology package indicates that fluralaner also has a sufficiently low acute toxicity profile to be consistent with SPF criteria for listing in Schedule 5. The acute poisoning risk to humans (in particular children) is low, partly associated with the proposed packaging of only four tablets in blister packaging. The delegate considered whether S4 listing could be more appropriate, providing for oversight of treatment by a veterinarian, noting that this is a condition imposed for registration in the USA, but in the end decided against this, on the basis that the treatment

[8] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

instructions are sufficiently clear that pet owners should be able to manage the required dosage regimen.

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

An early implementation date is proposed to facilitate marketing of the product when registered by the APVMA. The delegate therefore proposes an implementation date of 1 February 2015.

Scheduling entry

Schedule 5 – New entry

FLURALANER for the treatment and prevention of flea infestations and control of ticks in dogs in oral divided preparations each containing 1400 mg or less of fluralaner per dosage unit.

3.2 OCLACITINIB MALEATE

Scheduling proposal

In August 2014, the Office of Chemical Safety (OCS) referred, based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to register oclacitinib and to approve three different strengths of tablets, the following proposal to be considered by the delegate:

- A proposal to create a new Schedule 4 entry for oclacitinib.

The reasons for the request are:

- oclacitinib has moderate oral toxicity in rats (LD_{50} ~310 mg/kg bw in females);
- it has low dermal toxicity in rats (LD_{50} >2000 mg/kg bw);
- it has no skin irritation in rabbits;
- it is a severe eye irritant in rabbits; and
- it is not a skin sensitiser at concentrations ≤ 4% in mouse.

The OCS evaluation report indicated that no acute inhalational toxicity study was submitted for oclacitinib. While the acute inhalational toxicity is unknown, due to the general lack of specific toxicological data on the active constituent and formulation excipients, the lack of an acute inhalational toxicity endpoint is not considered a significant data deficiency and does not affect the risk assessment of the product, noting that the formulated product is in a film-coated tablet not expected to generate fine material of inhalational risk in this case.

Scheduling status

Oclacitinib is not specifically scheduled.

Scheduling history

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

Substance summary

Oclacitinib is an immunomodulator (a medicine that changes the activity of the immune system) that works by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the processes of inflammation and itchiness, including those involved in allergic and atopic dermatitis in dogs. By blocking the enzymes, the substance reduces the inflammation and itchiness associated with the disease[9]. The substance is intended for the treatment of clinical manifestations of pruritus associated with allergic dermatitis in dogs, and the treatment of clinical manifestations of atopic dermatitis in dogs.

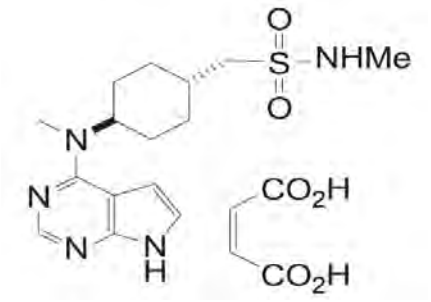

Figure 2. Structure of oclacitinib

Acute toxicity

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

Toxicity	*Species*	*Oclacitinib*	*SPF* Classification*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	310 (females)	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000 (no deaths)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Non-irritant	

[9] Apoquel Oclaticinib, European Medicines Agency. Available at [http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/veterinary/002688/WC500152068.pdf]

Toxicity	Species	Oclacitinib	SPF* Classification
Eye irritation	Rabbit	Severe irritant	
Skin sensitisation (Local Lymph Node Assay - LLNA)	Mice	Non-sensitiser at concentrations ≤ 4%	

**Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010)

The OCS evaluation report indicated that no acute toxicity studies for the tablet preparations (containing 3.6 mg, 5.4 mg and 16 mg of oclacitinib) have been submitted for evaluation. Estimation of product toxicity suggests that is a low acute oral and dermal toxicant, and not a skin irritant or sensitiser. Available data on eye irritation of the formulation components suggests that is likely to be irritating to eyes.

Repeat-dose toxicity

Repeat-dose oral toxicity studies in rats reported excessive toxicity and mortality at high doses (>100 mg/kg bw/day), with decreased red cell mass, myocardial degeneration, lymphoid depletion and hypocellularity in lymphoid tissue and bone marrow identified as treatment-related effects across all dose levels. Severity/frequency of findings showed broad dose level and/or dosing duration trends. Immunophenotyping reported changes in lymphocyte subpopulations, with alterations in cytotoxic T-cells, NKT and NK cells observed across dose levels attributable to the pharmacological effects associated with oclacitinib administration. A No Observed Effect Level (NOEL) was not established in rat studies, although it was noted that changes in clinical pathology, immunophenotyping and histopathology associated with lymphoid depletion generally occurred without evidence of clinical signs of toxicity at low doses.

In repeat-dose oral toxicity studies in dogs at up to 6 mg/kg bw/day, similar alterations in haematology, immunophenotyping and histopathology associated with lymphoid depletion and hypocellularity were consistently observed. No NOELs were established in dog studies. In an immunophenotyping study at 0.6 mg/kg bw for 15 weeks, treatment-related changes were observed in both blood and lymph node profiles, consistent with the pharmacological activity of the chemical. A short-term study in dogs dosed at 9 mg/kg bw twice daily reported clear T-cell inhibition and reticulocyte reductions associated with treatment, along with a range of other clinical pathology changes considered reversible after cessation of treatment.

A definitive margin-of-safety study in dogs (26 weeks at up to 5× the standard dose) suggested that oclacitinib was well tolerated in general, although observed effects in skin and lymph nodes were likely linked to the immunosuppressive nature of the chemical. Hypocellularity in lymphoid tissues and bone marrow was observed, consistent with other repeat-dose studies in the dog, although comparison of treatment-related effects in the repeat-dose dog studies suggested a general lack of progression in severity and frequency of identified effects.

Oclacitinib did not appear to affect the response of dogs to vaccination, with most immunosuppressive effects reversible after cessation of dosing; however, some clinical signs were still noted in some treated animals.

Mutagenicity

No information provided.

Genotoxicity

Oclacitinib was not genotoxic in an Ames and an *in vivo* micronucleus test. While no definitive carcinogenicity studies were available for evaluation, the lack of proliferative changes directly related to treatment in repeat-dose studies suggests that carcinogenicity is unlikely.

Carcinogenicity

No information provided.

Reproductive and developmental toxicity

Oclacitinib was not a developmental toxicant in both rat and rabbit. While skeletal variations and decreased foetal weights were identified in rat pups at 25 mg/kg bw/day (i.e. at doses where maternal toxicity was not observed), the OCS notes the lack of treatment-related malformations, and that treatment-related variations were consistent with developmental delays/maturity. In rabbits, malformations were identified only at doses with clear maternotoxicity (i.e. deaths and abortions at 60 mg/kg bw/day).

Observation in humans

No information provided.

Public exposure

Tablets containing oclacitinib for dogs will be administered primarily by pet owners and, therefore, management of potential domestic risks will need to be considered.

The main exposure to the substance will be by the dermal route. Residue levels resulting from the use of the product are expected to be negligible, as tablets are film coated and the excipients are widely used in approved veterinary/human pharmaceutical products. Noting that tablets are formulated such that formation of residues is unlikely, any resulting dermal-to-oral transfer of the product is also likely to be low. While the tablets are intended for division along the score line, the resulting exposure is also expected to be minimal, as formation of product dust is expected to be minimal.

The product is intended to be administered by adults and a tablet is not usually removed from the packaging until prior to administration. In addition, as the tablets will be contained in child resistant packaging, the likelihood of children accessing more tablets than the equivalent of a single dosing event is further limited. In the accidental oral ingestion scenario, where two 16 mg tablets (the maximum dose level as indicated for 55 to 80 kg dogs) are ingested by a 10 kg child, the exposure would be the equivalent of 3.2 mg/kg bw. For a 70 kg adult, the equivalent exposure is 0.46 mg/kg bw.

International regulations

No information provided. The Scheduling Secretariat has found the following information.

In May 2013, the US Food and Drugs Administration (FDA) approved the tablet preparations containing 3.6, 5.4 or 16 mg of oclacitinib as oclacitinib maleate per tablet. These preparations may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to rule out other diseases in the diagnosis of allergic and atopic dermatitis, and to monitor the safe use of the product, including the treatment of any adverse reactions.

In September 2013, the European Commission (EU) granted a marketing authorisation valid throughout the European Union, for Apoquel (containing the active substance oclacitinib at 3.5 mg, 5.4 mg and 16 mg doses).

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- OCS evaluation report (not publicly available);
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[10];
- Other relevant information.

Delegate's final decision

Oclacitinib, is an immunomodulator (a medicine that changes the activity of the immune system) that works by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the processes of inflammation and itchiness including those involved in allergic dermatitis and atopic dermatitis in dogs. By blocking the enzymes, the substance reduces the inflammation and itchiness associated with the disease. The substance is intended for the treatment of clinical manifestations of pruritus associated with allergic dermatitis in dogs, and treatment of clinical manifestations of atopic dermatitis in dogs. The listing of oclacitinib in Schedule 4 is based on the need for a veterinarian to diagnose and manage treatment of the condition. The OCS has recommended to the APVMA an appropriate set of label safety directions and warning statements about poisoning potential.

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

[10] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

An early implementation date is proposed to facilitate marketing of the product when registered by the APVMA. Therefore, the proposed implementation date is 1 February 2015.

Scheduling entry

Schedule4 – New entry

OCLACITINIB.

3.3 PYRIOFENONE

Scheduling proposal

In September 2014, the Office of Chemical Safety (OCS) referred, based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to register a new active ingredient namely pyriofenone, the following proposal to be considered by the delegate:

- A proposal to create a new Schedule 6 entry with no cut-offs for pyriofenone.

The reasons for the request are:

- pyriofenone has low acute oral, dermal and inhalational toxicity in rats;
- it is not a skin or eye irritant in rabbits;
- it is a skin sensitizer in Guinea pigs (Maximization test); and
- a reliable rabbit developmental toxicity study is not available.

Scheduling status

Pyriofenone, a fungicide in the aryl phenyl ketone chemical family, is not specifically scheduled. Another aryl phenyl ketone substance, metrafenone, is listed in Schedule 5 and Schedule 6. Preparations containing 50% or less of metrafenone are listed in Schedule 5 and all other preparations containing metrafenone are listed in Schedule 6.

Scheduling history

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

The scheduling history of metrafenone is provided below.

In February 2010, the National Drugs and Poisons Schedule Committee (NDPSC) considered a proposal to include metrafenone in a schedule. The NDPSC indicated that the key issue of concern was the carcinogenicity potential of metrafenone. Although carcinogenicity was observed in two species (which would normally indicate a Schedule 7 entry as being warranted), the carcinogenic response was only observed at very high dose rates and/or very high exposure rates. The NDPSC considered the relevance of the classification of metrafenone as a carcinogen to scheduling when such a high dose was required, and when, in practice, an individual would be highly unlikely to be exposed to such amounts. The NDPSC generally agreed, on the basis of the very low risk of being exposed to the quantities required for carcinogenicity, that the weight of evidence supported a Schedule 6, rather than Schedule 7 metrafenone parent entry. The NDPSC decided to include

preparations containing 50% or less of metrafenone in Schedule 5 and all other preparations containing the substance was listed in Schedule 6.

Substance summary

Pyriofenone belongs to a new chemical family called benzoylpyridines, discovered and developed for use in grapevines (and other arable and vegetable crops)[11].

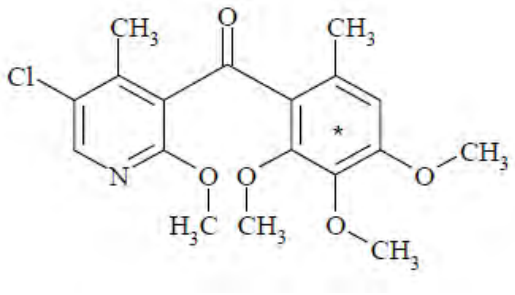

Figure 3. Structure of pyriofenone.

Acute toxicity

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

Toxicity	*Species*	*Pyriofenone*	*SPF* Classification*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000 (female, no deaths)	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000 (male and female no deaths)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>5180 (male and female, no deaths)	Low toxicity
Skin irritation	Rabbit	Non-irritant	
Eye irritation	Rabbit	Non- irritant	
Skin sensitisation (Guinea pig maximization test)	Guinea pig	Sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010)

[11] Pyriofenone: a novel powdery mildew fungicide for grapevine. Bernard, T.; Chantelot, E.; Ogawa, M. 10e Conférence Internationale sur les Maladies des Plantes, Tours, France, 3, 4 & 5 Décembre, 2012 2012 pp. 607-613. Available at http://cabdirect.org/abstracts/20133118253.html;jsessionid=777E399B144442A676AA7F14397D049A

Repeat-dose toxicity

For short-term to subchronic dietary studies with pyriofenone in rats, mice and dogs, the main target organs for toxicity were the liver and the kidneys (rats and mice only). At higher dosage levels, increases in caecum weight were also seen in rats. Mice were less susceptible to the toxicity of pyriofenone compared to rats and dogs, and kidney toxicity was seen at higher dose levels than liver toxicity. In rats and dogs, the no observed effect levels (NOELs) in subchronic dietary studies were 15.3 mg/kg bw/d and 20.6 mg/kg bw/d respectively, based on increased alkaline phosphatase activity and liver weight in dogs at 89.9 mg/kg bw/d, and increased activated partial thromboplastin time and decreased total bilirubin in rats at 69.0 mg/kg bw/d.

In chronic dietary studies, the liver and/or kidneys remained the main target organs in rat, mice and dogs, with treatment related effects also seen on blood clotting times in the rat and dog chronic studies. Additionally in dogs, at higher dose levels, vomiting and loose stool were observed.

The observed systemic toxicity and the dose levels at which these were observed do not warrant scheduling.

Mutagenicity

Pyriofenone was not mutagenic in bacteria and mammalian cells *in vitro* with and without metabolic activation, and did not induce chromosome aberrations or polyploidy in mammalian cells *in vitro* with and without metabolic activation at non-cytotoxic concentrations.

Genotoxicity

Pyriofenone did not induce micronuclei *in vivo* in the bone marrow of male and female mice up to and including the limit dose (2000 mg/kg bw). Thus, from the available data, pyriofenone is not an *in vivo* genotoxicant.

Carcinogenicity

In a rat 2-year dietary study, the overall incidences of all benign, malignant and combined benign and malignant tumours were comparable between treatment and control groups in both sexes. For specific tumour types, no statistically significant increase was seen, and a slight increase in the total incidence of combined hepatocellular adenomas and carcinomas in males at 5000 ppm (16% compared to 8% in controls) was seen at a dose level that produced an increase in unscheduled mortalities (i.e. liver tumours only seen in males at a dose level considered to have exceeded the maximum tolerated dose), and did not show a statistically significant dose-related trend when analysed by Peto's test.

In a mouse dietary 18-month study, for the total incidence of tumours, a statistically significant increase was seen in male mice only with ≥1 benign tumour(s) at 1800 (50%) and 5400 ppm (50%) compared to concurrent controls (31%). No historical control data on the laboratory incidence of such findings were provided, although historical control data were provided for specific tumour findings in the test laboratory. For specific tumour types, a statistically significant increase was only seen for combined hepatocellular adenomas and carcinomas in male mice at 5400 ppm (23.1% compared to 7.7% in controls), but this was within the historical control range (9.8 to 32.0% based on 11 studies), as were other (non-statistically significant) increases including the incidence of hepatocellular adenomas and carcinomas separately.

Consequently, there is no robust evidence that pyriofenone is carcinogenic in male and female rats and mice.

Reproductive toxicity

Pyriofenone was not a reproductive toxicant in a dietary 2-generation study in the rat up to and including dose levels that produced parental toxicity.

Developmental toxicity

In an oral (gavage) developmental toxicity study in rats, at 1000 and 300 mg/kg bw/d, an increased incidence was seen in the number of foetuses with skeletal variations (121/157 fetuses, 77.1% and 105/148 foetuses, 70.9% respectively). While no laboratory historical control data were provided on the incidence of foetuses with skeletal variations, such data were provided for specific skeletal variation in the strain of rat used in this developmental toxicity study. These historical control data have been used to interpret the observed skeletal findings and determine whether they are associated with pyriofenone treatment. Only the incidence of supernumerary rib at 1000 mg/kg bw/d (62.4%) was (slightly) outside the laboratory historical control range (35.7 to 61.0% based on 5 studies conducted from 2002 – 2008). Therefore, the findings at 1000 mg/kg bw/d were considered potentially treatment-related. However, these skeletal variations at the limit dose of 1000 mg/kg bw/d were seen in the presence of maternal toxicity (an increase in absolute and relative caecum weight) and are not sufficient for pyriofenone to be considered a hazard for developmental toxicity.

Only a preliminary dose-range finding developmental toxicity study (oral gavage) was available in the rabbit. In this study, observed abortions and premature deliveries at 1000 mg/kg bw/d, decreases in foetal and placental weight at 300 mg/kg bw/d and greater, and resorptions and foetal deaths at 100 mg/kg bw/d and greater, were seen in the presence of marked to severe maternal toxicity (i.e. during gestation, decreased body weight gain up to 16.2% at 100 mg/kg bw/d, and decreases in body weight gain >90.0% at 300 and 1000 mg/kg bw/d). Foetuses were only examined for external abnormalities, for which no treatment-related findings were seen. However, as this was a preliminary dose range finding study to identify dose levels for a subsequent definitive study (which was not submitted in the data package for this assessment), used low group sizes of 8 does per dose, and visceral and skeletal examination of the foetuses was not undertaken, it is not considered reliable for hazard identification. Thus, the absence of a developmental toxicity study in a second species constitutes a data gap (i.e. a deficiency in the data base) that needs to be taken into account when considering the potential scheduling of pyriofenone.

Observation in humans

No information provided.

Public exposure

No information provided.

International regulations

No information provided.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- OCS evaluation report (not publicly available);
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[12];
- Other relevant information.

Delegate's final decision

The toxicological profile of pyriofenone is well characterised. Based on the OCS evaluation report, this profile is consistent with either listing in Schedule 5 or 6. The acute and chronic toxicity profile is not remarkable and there is no evidence of appreciable skin-eye irritancy. The primary reason for considering Schedule 6 to be more appropriate is potential for sensitisation, and an identified data gap in that a developmental toxicity study in a second species has not yet been submitted. The delegate has accepted the OCS recommendation that pyriofenone be listed in Schedule 6, with no cut-off.

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

An early implementation date is proposed to facilitate clearance of the active ingredient by the APVMA and prior to consideration of any products based on pyriofenone. Therefore, the proposed implementation date is 1 February 2015.

Scheduling entry

Schedule 6 – New entry

PYRIOFENONE.

[12] National Coordinating Committee on Therapeutic Goods (NCCTG): Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]