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

November 2015

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

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

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the March 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#13);
- scheduling proposals initially referred to the August 2015 meetings of the Advisory Committee on Chemicals Scheduling (ACCS#14); and
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to expert advisory committee

Pre-meeting public notice

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 29 January 2015 and the second public notice was published on 4 June 2015 at Consultation: Invitation for March 2015 meeting and March 2015 Delegate's Interim Decisions and Consultation Invitation, respectively.

Edited versions of the public submissions received in response to the invitation were published on 4 June 2015 at Public Submissions Scheduling Matters.

Interim decisions

The delegate's interim decisions, on recommendations by the ACCS#13 and ACCS#14, were published on 4 June 2015 and 1 October 2015 respectively on the TGA website. 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 have been considered by the delegate.

Edited versions of valid public submissions received in response to the interim decisions will be published after 19 November 2015 and will be available at Chemical Scheduling Submissions.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either, confirming, varying or setting aside the interim decision, but only after considering any valid submissions and relevant information 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 Medicines and Chemicals* (SPF, 2015), available at Scheduling Policy Framework.

Publishing of the amendments to the Poisons Standard

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

Privacy and your personal information

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

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

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

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

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

Glossary

Abbreviation	Name
ADI	Acceptable daily intake
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute reference dose
CAS	Chemical Abstract Service
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FDA	Food and Drug Administration (United States)
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
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
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level

Abbreviation	Name
NOHSC	National Occupational Health & Safety Commission
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])
OET	Open Epicutaneous Test
PEC	Priority existing chemical
PI	Product Information
PIC	Poisons Information Centre
QRA	Quantitative Risk Assessment
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety
SS	Standard statement
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
WHO	World Health Organization
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 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#13)

Summary of delegate's final decisions

Substance	Final decision
2-ethylhexanoic acid and its derivatives	***Schedule 6—New Entry*** 2-ETHYLHEXANOIC ACID and its alkyl esters except in preparations containing 5 per cent or less calculated as 2-ethylhexanoic acid. ***Appendix E, Part 2—New Entry*** 2-ETHYLHEXANOIC ACID Standard Statement: A ***Appendix F, Part 3—New Entry*** 2-ETHYLHEXANOIC ACID Warning Statement: 53 ***Schedule 6, Appendix E and Appendix F—Delete entries*** 2-ETHYLHEXYL 2-ETHYLHEXANOATE *Implementation date: 1 February 2016.*
4,5-dichloro-2-octyl-3(2H)-isothiazolone	In response to the interim decision, the applicant submitted additional information. For appropriate consideration of the additional information this matter will be referred back to the ACCS for further advice. Since the interim decision was to make no change to the current Schedule6 listing, that decision stands, pending consideration of the additional submitted information by the ACCS and the delegate.

1.1 2-ethylhexanoic acid and its derivatives

Scheduling proposal

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

- That a new entry be created in Schedule 6 for 2-ethylhexanoic acid and its derivatives, with appropriate low concentration exemption cut-off in cosmetic and/or domestic preparations containing esters that hydrolyse and/or metabolise to 2-ethylhexanoic acid.

In December 2014, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment Prioritisation (IMAP) programme, referred the following proposal to be considered by the chemicals scheduling delegate:

- That a new entry be created in Schedule 6 for 2-ethylhexanoic acid and its derivatives, with appropriate low concentration exemption cut-off in cosmetic and/or domestic preparations containing esters that hydrolyse and/or metabolise to 2-ethylhexanoic acid.

The reasons for the request were:

- 2-Ethylhexanoic acid is not directly used in cosmetic or domestic products in Australia. Ester derivatives of the chemical readily hydrolyse to form 2-ethylhexanoic acid via chemical or enzymatic processes, and this was accepted by the Delegate as a basis for scheduling 2-ethylhexyl 2-ethylhexanoate at concentrations above 10% (which is broadly equivalent to 5% 2-ethylhexanoic acid). The Cosmetic Ingredient Review's (CIR) assessment of alkyl ethylhexanoates (CIR, 2013) indicates that alkyl ethylhexanoates have widespread use in cosmetic products overseas. It is expected that these ester derivatives have similar uses in cosmetic products in Australia.
- Sixteen cosmetic ingredients which metabolise to 2-ethylhexanoic acid are identified from CIR, 2013. These compounds are best scheduled as derivatives of 2-ethylhexanoic acid, which is the toxic species of concern.
- Scheduling the derivatives based on the percentage that can be metabolized to 2-ethylhexanoic acid will result in uniform treatment.
- The critical health effects of 2-ethylhexanoic acid include systemic long-term effects (fertility and developmental toxicity) based on observations in laboratory animals. Fertility effects (reduction in sperm motility, abnormal sperm, and dose-dependent delays in mating) were reported in rats. Developmental toxicity effects were noted in the absence of maternal toxicity from several studies in rats following exposure to the chemical via the oral route. The lowest observed adverse effect level (LOAEL) was reported to be 100 mg/kg bw/day based on skeletal variations (wavy ribs) and skeletal malformations (club foot) of the foetuses.
- There are currently no labelling requirements for products containing the chemical and its derivatives (apart from 2-ethylhexyl 2-ethylhexanoate) in Australia. However, the characterised critical health effects (fertility and developmental toxicity) have the potential to pose an unreasonable risk to the public under the uses identified.

Delegates reasons for referring this to the committee

The related substance, 2-ethylhexyl 2-ethylhexanoate was considered by the ACCS at the July 2014 meeting. The key toxicological issue was reproductive toxicity associated with the hydrolysis of this ester to known reproductive toxicants, 2-ethylhexanol and 2-ethylhexanoic acid. The current IMAP report recommends making a separate Schedule 6 entry, with appropriate low-level cut-offs to regulate the use of 2-ethylhexanoic acid, but more particularly, esters that hydrolyse to form this known reproductive toxin.

The delegate asked the ACCS the following questions:

- The NICNAS IMAP report suggests there are likely to be few products where 2-ethylhexanoic acid may be a direct ingredient, but there are potentially more esters used in cosmetic and domestic products. The 2013 US CIR Expert Panel report lists some 16 alkyl esters of 2-ethylhexanoic acid used in cosmetic products that could be hydrolysed to 2-ethylhexanoic acid. Does the ACCS support a Schedule 6 listing that captures all these esters? What wording of the Schedule 6 entry would best capture such a generic listing?
- The current Schedule 6 entry for 2-ethylhexyl 2-ethylhexanoate is: 2-ETHYLHEXYL 2-ETHYLHEXANOATE **except** in preparations containing 10 per cent or less of 2-ethylhexyl 2-ethylhexanoate. There are also entries in Appendices E & F. These entries would become redundant in the light of a generic entry. Should they be deleted or retained?
- The 10% cut-off to exempt has apparently been recommended for consistency with the 10% exemption in the generic S6 entry for ethylene glycol monoalkyl ethers and their acetates (also a

reproductive toxicity issue). Is this cut-off suitable for a generic entry for 2-ethyhexanoates? The 10% cut-off recommended for 2-ethylhexyl 2-ethylhexanoate would represent approximately 5% of the hydrolysed acid. Is it possible to word a generic S6 entry so that it only captures the hydrolysis products of esters at a relevant concentration?

- The CIR report suggest that current uses of alkyl esters of 2-ethylhexanoic acid used in cosmetic products at concentrations up to 77% in rinse-off products and 53% in leave-on products is 'safe'. What impact does this report have on a proposal to develop a generic listing with one or more exemption cut-offs for leave-on or rinse-off cosmetic products?

- If a generic listing is impractical, would a simple entry for 2-ethylhexanoic acid and its derivatives, with a 5% exemption cut-off, have any regulatory effect? Would such an entry capture any or all of the alkyl esters as 'derivatives'?

Substance summary

Refer to the NICNAS IMAP human health Tier II assessment report for *Hexanoic acid, 2-ethyl-*. This report is publicly available on the NICNAS website: NICNAS IMAP assessment report ID 787. A summary is provided below.

In addition, the CIR assessment of alkyl ethylhexanoates (CIR, 2013) is publicly available from CIR assessment.

Repeat-dose toxicity

In a 90-day dietary study in rats, a LOAEL of 917 mg/kg bw/day was reported based on reduced body weight gain in conjunction with reduced feeding (Canada, 2011). A lowest observed effect level (LOEL) of 303 mg/kg bw/day was also reported based on increased relative liver weight and hepatocyte hypertrophy.

In a 90-day dietary study in mice, a LOAEL of 1040 mg/kg bw/day was reported based on reduced body weight (Canada, 2011; REACH). A LOEL of 885 mg/kg bw/day was also reported based on effects including increased relative liver weight, hepatocyte hypertrophy, kidney effects and forestomach lesions.

Reproduction and developmental toxicity

The chemical is classified as hazardous as a Category 3 reproductive toxin with the risk phrase 'Possible risk of harm to the unborn child' (Xn; R63) in Safe Work Australia's Hazardous Substances Information System (HSIS). There is also sufficient evidence to classify the chemical as potentially toxic in relation to fertility.

The chemical was reported to cause developmental toxicity in several studies in rats following exposure via the oral route (Canada, 2011; Pennan et al., 1992; REACH). These effects were noted in the absence of signs of maternal toxicity. The lowest developmental toxicity LOAEL was reported to be 100 mg/kg bw/day.

In a developmental toxicity study, pregnant female Wistar rats were administered the chemical on gestation days 6–19 via drinking water at 0, 100, 300 or 600 mg/kg bw/day (Canada, 2011; Pennan et al., 1992; REACH). Skeletal variations in foetuses were observed at the lowest dose. A dose-dependent increase in club foot was observed in foetuses of the treatment group (statistically significant at the highest and intermediate dose); this anomaly was not observed in any foetuses of the control group. A statistical increase in wavy ribs was also observed in the foetuses of all treatment groups compared to controls. A dose-dependent increase in malformation of the legs, reported as 'flabby legs (external, slightly paralysed)' was also observed in foetuses of all treatment groups; this was not observed in any foetuses of the control group. While a maternal toxicity LOAEL of 600 mg/kg bw/day (highest dose) was reported from this study, based on decreased maternal body weight gain (Canada, 2011; Pennan et al., 1992), a REACH dossier reported maternal toxicity (slightly lower pregnancy rates and reduced body weights) at 300 mg/kg bw/day. A developmental LOAEL of 100 mg/kg bw/day was determined from this study in both reports.

Foetal skeletal variations, malformations, reduced foetal body weights and early foetal deaths have also been reported in several other developmental toxicity studies in rats following oral exposure to the chemical (Canada, 2011; REACH). For each of these studies, developmental effects were observed in the absence of maternal toxicity.

In a reproductive toxicity study in Wistar rats, the sodium salt of the chemical was administered via drinking water at 100, 300 or 600 mg/kg bw/day (Pennan et al., 1993; REACH). Males were exposed to the chemicals for 10 weeks prior to mating and for three weeks during mating; females were exposed for two weeks prior to mating and throughout the entire gestation and lactation period. Effects on the male reproductive system (reduction in sperm motility) were observed at 100 mg/kg bw/day, and increases in abnormal sperm were observed at 300 and 600 mg/kg bw/day. Dose-dependent delays in mating at 300 and 600 mg/kg bw/day were also reported, in addition to some animals being reported to be 'totally infertile'.

Public exposure

While use of the chemical in domestic products in Australia is not known, it is reported to be used in domestic products overseas. Limited information with regard to concentration in domestic products is available from the US National Library of Medicine's Household Products Database, which indicated use of the chemical in:

- liquid form auto products (antifreeze) at up to 8%;
- a home maintenance product (paint drier) at up to 5%; and
- an arts and craft stain product at less than 4%.

An approximate margin of exposure (MOE) was calculated by Canada (2011) based on domestic use of the chemical in similar types of products identified in this report (alkyd paints), using similar levels of bioavailability, and LOAELs. The calculations resulted in the determination that the MOE was acceptable, particularly given the expected episodic exposure of the general population to the chemical from normal use of these products.

However, since esters that hydrolyse and/or metabolise to 2-ethylhexanoic acid are widely available to the general public, appropriate restrictions on the chemical and its derivatives are needed.

International regulations

The chemical is listed on the following:

- European Union Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the composition of cosmetic products.
- New Zealand Cosmetic Products Group Standard – Schedule 4: Components cosmetic products must not contain.

Scheduling status

2-Ethylhexanoic acid is not specifically scheduled.

Scheduling history

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

However, a chemical belonging to the same group of chemicals, namely 2-ethylhexyl 2-ethylhexanoate was considered by the ACCS in March 2014. The delegate decided to include this chemical in Schedule 6 due to reproductive/developmental toxicity associated with its ready hydrolysis to the known reproductive toxicants, 2-ethylhexanol and 2-ethylhexanoic acid.

Schedule 6

2-ETHYLHEXYL 2-ETHYLHEXANOATE **except** in preparations containing 10 per cent or less of 2-ethylhexyl 2-ethylhexanoate.

Appendix E, Part 2

Poisons	Standard statements
2-Ethylhexyl 2-ethylhexanoate	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).

Appendix F, Part 3

Poisons	Warning statements	Safety direction
2-Ethylhexyl 2 ethylhexanoate	53. CAUTION – 2-ethylhexyl 2-ethylhexanoate should not be used by pregnant women.	

Pre-meeting public submissions

One public submission was received. The submission proposed that 2-ethylhexanoic acid should be included in Schedule 6, except when in concentrations of 10% or less, to be consistent with the scheduling decision for 2-ethylhexyl-2-ethylhexanoate (2-EHEH) made in August 2014. The submission noted that the Appendix E and F statements used for 2-EHEH are also relevant for 2-ethylhexanoic acid and should be maintained. The following schedule entry for esters of 2-ethylhexanoic acid was also proposed:

> ALKYL ETHYLHEXANOATES (excluding derivatives) in preparations containing 10 percent or more alkyl ethylhexanoate calculated as 2-ethylhexanoate.

Summary of ACCS advice to the delegate

The committee recommended that a new Schedule 6 entry be created for 2-ethylhexanoic acid with exceptions in preparations containing 5 per cent or less of as calculated as 2-ethylhexanoic acid.

The committee also recommended a new Appendix E, Part 2 entry (standard statement A) and a new Appendix F, Part 3 entry (warning statement 53).

In addition, the committee recommended the current Schedule 6 and Appendices E and F entries for 2-ethylhexyl 2-ethylhexanoate be deleted.

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

The reasons for the recommendation comprised the following:

- Developmental toxicant.
- Alkyl esters are used in cosmetic products which in vivo hydrolyse to the acid which is the toxin.

Delegate's interim decision

The delegate accepts ACCS advice that the recent scheduling decision to include 2-ethylhexyl-2-ethylhexanoate in Schedule 6, because of the reproductive toxicity potential of its hydrolysed acid and alcohol components, needs to be broadened to capture all the alkyl 2-ethylhexanoate esters that can yield 2-ethylhexanoic acid via hydrolysis. The delegate notes the advice from NICNAS and the actions

by other regulators to limit the concentrations of such esters in cosmetic products that are applied directly to human skin. The issue considered by the ACCS was how to word a generic entry in Schedule 6 to capture these esters. ACCS advice was that, while 2-ethylhexanoic acid was unlikely to be used in cosmetics or other products as itself, including **its alkyl esters** in the entry could ensure that all the substances of concern would be captured. The exemption cut-off (5%) could then be based on the amount of 2-ethylhexanoic acid able to be released by complete hydrolysis. It is possible that a simple Schedule 6 entry for 2-ethylhexanoic acid could capture the alky esters as 'derivatives', consistent with guidance in Part 1 of the Poisons Standard, but the proposed wording should be clearer in its coverage and provide a consistent exemption cut-off for substances that contain 2-ethylhexanoic acid in different proportions based on molecular weights.

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

Schedule entry

Schedule 6 – New Entry

2-ETHYLHEXANOIC ACID and its alkyl esters **except** in preparations containing 5 per cent or less calculated as 2-ethylhexanoic acid.

Appendix E, Part 2 – New Entry

Poison	Standard Statement
2-ethylhexanoic acid and its alkyl esters	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 1126; New Zealand 0800 764 766) or a doctor (at once).

Appendix F, Part 3 – New Entry

Poison	Warning Statement	Safety Directions
2-ethylhexanoic acid and its alkyl esters	53 – CAUTION – (Name of substance) should not be used by pregnant women.	

Schedule 6, Appendix E and Appendix F – Delete Entries

2-Ethylhexyl 2-ethylhexanoate.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

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

Public submissions on the interim decision

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

An edited version of the submission is available on the TGA website at: Public Submissions ACCS #13 March 2015.

Delegate's final decision

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

The proposed implementation date is 1 February 2016. This is the earliest date of which the projected publication of an update to the SUSMP would allow for implementation in the State/Territory legislation.

1.2 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone

Scheduling proposal

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

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

The applicant's reasons for the request were:

- 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone is a film biocide used in paints, jointing compounds and sealants to provide fungicide protection to stop the growth of mould. Given the nature of these products, their packaging and use, oral ingestion of any significant amounts of the formulated product is unlikely. The proposed exemption cut-off concentration of 0.12% is low, exposure would be accidental and based on the pharmacology of the substance, any associated absorption would be minimal with clearance within 2 days and no evidence of accumulation once absorbed.

- The proposal aims to provide 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone with an exemption from scheduling in the same manner that specified concentrations of carbendazim and octhilinone are exempt. Carbendazim and octhilinone have been extensively considered by scheduling committees over a 40 year period. Hence, there is considerable precedent related to this proposal and the relevant matters under 52E(1): the risks and benefits, potential hazards, extent and patterns of use and dosage and formulation have previously been considered for carbendazim and octhilinone resulting in exemption cut-offs for both substances.

- On the basis of the toxicological data presented in this submission, 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is a safer, suitable alternative film biocide to carbendazim (excluded from Schedule 7 at 0.1% or less) and is an isothiazolinone structurally-related to the film biocide octhilinone (excluded from Schedule 6 at 1% or less); however, without an exemption from Schedule 6, 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is not regulated in the same manner as carbendazim and octhilinone.

Delegates reasons for referring this to the committee

This application to vary the current Schedule 6 entry for 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone has some elements in common with the scheduling consideration of methylisothiazolinone and methylchloroisothiazolinone. The common element is the potential for skin sensitisation and where to set an appropriate cut-off from the existing Schedule 6 listing. The different element is that the proposed cut-offs relate to products that are not directly applied to the skin in cosmetics. Also, the current S6 schedule entry for octhilinone, a thiazolone preservative with a comparable toxicological

profile, may provide a useful template and support for an amended schedule 6 entry for 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone.

The delegate asked the ACCS the following questions:

- The applicant has provided skin irritancy/sensitisation test data in support of the proposed exemption cut-off, and these test data have been evaluated by the OCS. Does the ACCS agree that these data support the proposed 0.12% cut-off for paints, jointing compounds and sealant preparations? Note that the OCS evaluation report and references to European Commission assessments suggest a much lower threshold for sensitisation.
- Is it necessary to develop a separate exemption sub-clause for paints, so that the concentration can be specified as calculated on the non-volatile content of the paint?
- Can the ACCS advise whether the proposed uses of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone are consistent with the Appendix A exemption for *ALGICIDES, BACTERIOCIDES OR SLIMICIDES for industrial use that do not fit the definition of an agvet product?* A search of the Australian Pesticide and Veterinary Medicines Authority (APVMA) PUBCRIS database reveals no registered products containing this ingredient. [Note: there are also no APVMA-registered products containing octhilinone on PUBCRIS, although it is registered as an approved active ingredient].

Substance summary

4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone is an industrial biocide. It is a broad spectrum antifungal biocide used in paints, coatings, silicone sealants, plastics and for marine antifouling applications as well as the preservation of wood, masonry and other construction products.

Depending on the concentration used, 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone can act as a fungicide/fungistat, bactericide/bacteristat and/or algaecide/algicstat.

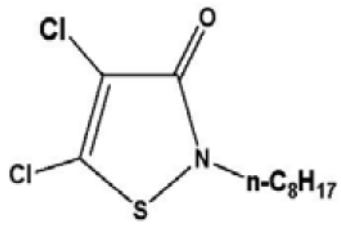

Figure 1: Structure of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone

Acute toxicity

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

Toxicity	Species	4,5-Dichloro-2-N-octyl-3(2h)-isothiazolone	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Mouse	567 mg/kg	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	> 2000 mg/kg (in xylene)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/L/4h)	Rat	0. 22 mg/L (in xylene)	High to extremely high toxicity

Toxicity	Species	4,5-Dichloro-2-N-octyl-3(2h)-isothiazolone	SPF Classification
Skin irritation	Rabbits	Corrosive (in xylene).	
Eye irritation	Not provided	Corrosive (in xylene) based on skin irritation end-point.	
Skin sensitisation (Magnusson-Kligman Method)	Guinea pigs	Skin sensitiser	

Toxicity assessment

The Office of Chemical Safety (OCS) conducted an assessment of the information provided by the applicant. Based on the available studies, OCS concluded that the chemical is a skin sensitiser in guinea pigs even at the lowest concentration tested (<0.12%) and with a small area of exposure at induction and challenge at remote site. The OCS concluded that the new skin sensitisation study submitted with the application confirms that the chemical is a strong sensitiser and therefore warrants a Schedule 6 entry. There was no evidence provided to support a cut-off concentration of 0.12% or lower.

Observation in humans

No information provided.

Public exposure

The wood preservative is to be used for preventative application by industrial techniques (automated spraying, flow coating, automated dipping, vacuum/pressure and double vacuum treatment). The Applicant has indicated that a future use could be in ready to use formulations for professional *in situ* use. Such future use has not been considered.

Professionals may be exposed when handling or processing treated wood (secondary exposure). The general public may be exposed during handling/contact with treated wood (secondary exposure).

Dermal exposure and exposure by inhalation are the main exposure routes.

International regulations

In September 2007, the US Environmental Protection Authority (US EPA) determined that 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone is eligible for reregistration provided that additional required data confirm this decision, the risk mitigation measures outlined in the document are adopted, and label amendments are made to reflect these measures.

In April 2014, the European Union (EU) released an approval notice for 4,5-dichloro-2-octyl-2H-isothiazol-3-one with the approval date for the substance of 1 January 2016. The approval of the substance has the following specific conditions:

- The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.
- Persons making products containing 4,5-Dichloro-2-octyl-2H-isothiazol-3-one available on the market for non-professional users shall make sure that the products are supplied with appropriate gloves.

Authorisations are subject to the following conditions:

1. For industrial or professional users, safe operational procedures and appropriate organizational measures shall be established. Where exposure cannot be reduced to an acceptable level by other means, products shall be used with appropriate personal protective equipment.

2. Labels and, where provided, instructions for use shall indicate that children shall be kept away until treated surfaces are dry.

3. Labels and, where provided, safety data sheets of products authorised shall indicate that application, maintenance and repair activities shall be conducted within a contained area, on impermeable hard standing with bunding or on soil covered with an impermeable material to prevent losses and minimize emissions to the environment, and that any losses or waste containing 4,5-Dichloro-2-octyl-2H-isothiazol-3-one shall be collected for reuse or disposal.

4. For products that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council (3) or Regulation (EC) No 396/2005 of the European Parliament and of the Council (4) shall be verified, and any appropriate risk mitigation measures shall be taken to ensure that the applicable MRLs are not exceeded.

5. Where an article has been treated with or intentionally incorporates one or more biocidal products containing 4,5-dichloro-2-octyl-2H-isothiazol-3-one and where necessary due to the possibility of skin contact as well as the release of 4,5-dichloro-2-octyl-2H-isothiazol-3-one under normal conditions of use of the article, the person responsible for placing the article on the market shall ensure that the label provides information on the risk of skin sensitisation, as well as the information referred to in the second subparagraph of Article 58(3) of Regulation (EU) No 528/2012.

Scheduling status

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

Schedule 6

4,5-DICHLORO-2-N-OCTYL-3(2H)-ISOTHIAZOLONE.

Scheduling history

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

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommends that the proposal is not supported and the current scheduling of 4,5-Dichloro-2-N-octyl-3(2H)-isothiazolone remains appropriate.

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

The reasons for the recommendation comprised the following:

· Severe potential for skin sensitisation

Delegate's interim decision

The delegate accepts the advice of the ACCS that the current Schedule 6 entry for 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone (DCIT) remains appropriate.

The key issues driving the scheduling of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone are its potential for skin/eye corrosivity and skin sensitisation. An evaluation of submitted test data suggested that skin irritation and sensitisation can be demonstrated to occur at concentrations much lower than the 0.12% in the products under consideration. Accordingly, the delegate is unable to determine a concentration at which a product could be exempted to a lower schedule.

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

The delegate agrees that the current Schedule 6 entry remains appropriate.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

Two submissions were received. One submission did not support the delegate's interim decision, and provided further toxicological data in support of the scheduling proposal. The second submission did not comment on the scheduling proposal specifically rather the submission commented in general terms on the scheduling of biocides used in paint production in Australia.

An edited version of the submission is available on the TGA website at: Public Submissions ACCS #13 March 2015.

Delegate's final decision

In response to the interim decision, the applicant submitted additional information. For appropriate consideration of the additional information this matter will be referred back to the ACCS for further advice. Since the interim decision was to make no change to the current schedule 6 listing that decision stands, pending consideration of the additional submitted information by the ACCS and the delegate.

The delegate notes the comments made in a submission relating to the use of industrial biocides. The delegate has made no determination on whether the use of 4,5-dichloro-2-N-octyl-3(2H)-isothiazolone as an industrial biocide is consistent with exemption from scheduling under the provisions of Appendix A. This is a matter for individual State/Territory jurisdictions in interpreting their legislation. However, the delegate notes the points made in the public submission relating to the need for harmonisation of regulatory approaches to industrial biocides and the ACCS recommendation that the relevant entry in Appendix A may need to be reviewed. This matter will also be referred back to the ACCS for consideration at the next available meeting.

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

2. Scheduling proposals referred to the August 2015 ACCS meeting

Summary of delegate's final decisions

Substance	Final decision
Cyclopropylmethyl, 3-hexanoate	Does not require scheduling.
Bicyclopyrone	***Schedule 6—New Entry*** BICYCLOPYRONE except when included in Schedule 5. ***Schedule 5—New Entry*** BICYCLOPYRONE in preparations containing 20 per cent or less of bicyclopyrone. *Implementation date: 1 February 2016*
Clitoria ternatea extract	***Appendix B—New Entry*** CLITORIA TERNATEA EXTRACT. Subject to: (a) low toxicity; 1.2: insecticide. *Implementation date: 1 February 2016*
Cyclopentane, alpha,alpha-dimethylpropanol	Does not require scheduling.
Hydramethylnon	The current scheduling for hydramethylnon remains appropriate.
Momfluorothrin	**Schedule 6—New Entry** MOMFLUOROTHRIN *Implementation date: 1 February 2016*
Carcinogenic amines (Azo dyes)	**Schedule 7—New Entry** AZO DYES that are derivatives by diazotisation of any of the following substances: · o-anisidine (CAS No. 90-04-0) · o-toluidine (CAS No. 95-53-4) · p-aminoazobenzene (CAS No. 60-09-3) · o-aminoazotoluene (CAS No. 97-56-3) · 2,4-toluenediamine (CAS No. 95-80-7) · 5-nitro-o-toluidine (CAS No. 99-55-8) · p-chloroaniline (CAS No. 106-47-8)

Substance	Final decision
	· 4-chloro-o-toluidine (CAS No. 95-69-2) *Implementation date: 1 February 2016*
Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)	Does not require scheduling.
4-amino-m-cresol (Phenol, 4-amino-3-methyl)	***Schedule 6—New Entry*** 4-AMINO-*M*-CRESOL in hair dyes and eyebrow/eyelash colouring preparations **except**: a) in hair dye preparations containing 1.5 per cent or less of 4-amino-*m*-cresol after mixing for use when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. Written in letters not less than 1.5mm in height; or b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-*m*-cresol after mixing for use when the immediate container and primary pack are labelled with the following statement: WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. Written in letters not less than 1.5mm in height. **Appendix E—New Entry** 4-AMINO-*M*-CRESOL Standard statements: A, E1 **Appendix F—New Entry** 4-AMINO-*M*-CRESOL Warning Statement: 28 *Implementation date: 1 June 2016*
4-amino-2-hydroxytoluene (Phenol, 5-amino-2-methyl)	**Schedule 6—New Entry** 4-AMINO-2-HYDROXYTOLUENE in hair dyes and eyebrow/eyelash

Substance	Final decision
	colouring products **except**: a) in hair dye preparations containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. Written in letters not less than 1.5mm in height; or b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statement: WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. Written in letters not less than 1.5mm in height. **Appendix E—New Entry** 4-AMINO-2-HYDROXYTOLUENE Standard statements: A, E1 **Appendix F—New Entry** 4-AMINO-2-HYDROXYTOLUENE Warning Statement: 28 **Index—New Entry** 5-AMINO-*O*-CRESOL see 4-AMINO-2-HYDROXYTROLUENE *Implementation date: 1 June 2016*
2-amino-6-chloro-4-nitrophenol (Phenol, 2-amino-6-chloro-4-nitro)	**Schedule 6—New Entry** 2-AMINO-6-CHLORO-4-NITROPHENOL in hair dye and eyebrow/eyelash colouring preparations, **except**: a) in preparations containing 2 per cent or less of 2-amino-6-chloro-4-nitrophenol when applied directly to the hair, or containing 2 per cent or less of 2-amino-6-chloro-4-nitrophenol after mixing and when the immediate container and primary pack are labelled with the following

Substance	Final decision
	statements: KEEP OUT OF REACH OF CHILDREN; and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. Written in letters not less than 1.5mm in height. b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 2-amino-6-chloro-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statement: WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. Written in letters not less than 1.5mm in height. **Appendix E—New Entry** 2-AMINO-6-CHLORO-4-NITROPHENOL Standard statements: A, E1 **Appendix F—New Entry** 2-AMINO-6-CHLORO-4-NITROPHENOL Warning Statement: 28 *Implementation date: 1 June 2016*

2.1 Cyclopropylmethyl, 3-hexenoate

Scheduling proposal

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

- In April 2015, the delegate received a request to consider creating a new entry for cyclopropylmethyl, 3-hexenoate in Schedule 6 when used in cosmetic and household products, except when used at appropriately low usage concentrations.

Scheduling application

The reasons for the request were:

- The chemical has moderate to high acute oral toxicity, consistent with the Schedule 6 factors.
- The chemical presents a moderate-high hazard from repeated use.

Delegates reasons for referring this to the committee

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

The delegate asked the committee the following questions:

- Does the ACCS consider that the toxicological profile of cyclopropylmethyl, 3-hexenoate is sufficiently similar to the seven fragrance chemicals where no scheduling action was recommended, or is it more like 4,4-dimethyl-1-cyclohexene-1 propanal, where listing in Schedule 6 was recommended, along with different product-related exemption cut-offs?
- If scheduling is recommended, is the chemical name cyclopropylmethyl, 3-hexenoate the preferred name for listing (or some other name)?
- Does the ACCS support different exempt cut-offs for a Schedule 6 entry for different product types, as proposed in the NICNAS report?

Substance summary

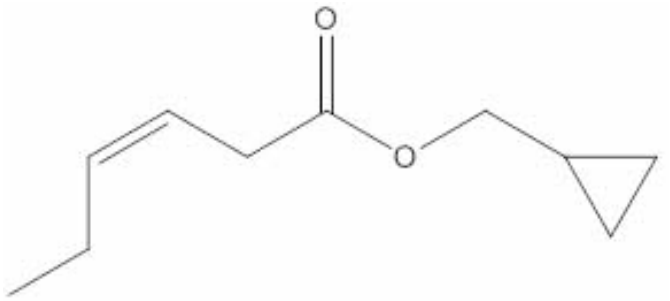

Figure 1. Structure of Cyclopropylmethyl, 3-hexenoate

Acute toxicity

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

Toxicity	Species	Cyclopropylmethyl, 3-Hexenoate	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	300-2000	Consistent with Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000	None
Acute inhalation toxicity LC_{50} (mg/L/4h)	Rat	> 5.18	None

Toxicity	Species	Cyclopropylmethyl, 3-Hexenoate	SPF Classification
Skin irritation	Rabbit	Slightly irritating	None
Eye irritation	Rabbit	Slightly irritating	None
Skin sensitisation (Local lymph node assay)	Mouse	No evidence of sensitisation	None

Repeat dose toxicity

An NOAEL of 30 mg/kg bw/day was established in a 28 day repeat dose oral toxicity study in rats. The study was conducted at dose levels of 30, 100 and 300 mg/kg bw/day, with adverse effects in the heart and liver noted in animals treated at ≥ 100 mg/kg bw/day. Additional effects in the stomach, testes, epididymis, female reproductive organs and eyes were observed in animals treated at 300 mg/kg bw/day.

Mutagenicity

The chemical was not mutagenic in a bacterial reverse mutation assay.

Genotoxicity

The chemical was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 0.05% concentration) through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposures (e.g. through the use of spray products) are also possible.

International regulations

No information was provided.

Scheduling status

Cyclopropylmethyl, 3-hexenoate is not specifically scheduled.

Scheduling history

Cyclopropylmethyl, 3-hexenoate has not been previously considered for scheduling; therefore, scheduling history is not available. However, for the one fragrance ingredient where the ACCS did recommend scheduling (see notes below), the wording used in the listing was:

Schedule 6—New Entry

Cyclopropylmethyl, 3-hexenoate **except**:

a) when used in fine fragrances at a concentration of 0.05 per cent or less;

b) when used in other cosmetic products at a concentration of 0.03 per cent or less;

c) when used in household products at a concentration of 0.05 per cent or less.

Reasons for the suggested cut-offs

As stated above, the NICNAS recommended usage concentrations of 0.05 per cent in fine fragrances, 0.03 per cent in other cosmetic products and 0.05 per cent in household products correspond to the maximum proposed usage concentrations by the notifier. The NICNAS assessment determined that there was no unreasonable risk to the public when used at these concentrations.

Pre-meeting public submissions

One public submission was received. The submission proposed that it is unnecessary to schedule Cyclopropylmethyl, 3-hexenoate. The reason given was that there is in place an international standard of scheduling fragrances, imposed by the International Fragrance Association (IFRA), and companies internationally already comply with this standard.

The public submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The Committee recommended a new Schedule 6 entry be created for cyclopropylmethyl, 3-hexenoate with except in preparations containing 0.05 per cent or less.

The committee recommended an implementation date of 1 February 2016.

The committee also recommended changing the name from its original reference of 3-hexanoic acid, cyclopropylmethyl ester to CYCLOPROPYLMETHYL, 3-HEXENOATE.

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

The reasons for the recommendations comprised the following:

· Meets the criteria for schedule 6

· Restricting to a cut-off of 0.05 per cent. The risk to public health at very low concentrations is minimal

Delegate's interim decision

Not to schedule this substance.

The reasons for the interim decision comprised the following:

The delegate notes that the ACCS advice to include this fragrance ingredient in Schedule 6 is based primarily on the fact that its acute toxicity, but not skin/eye irritancy or sensitisation potential is consistent with SPF criteria for listing in Schedule 6, and that a 0.05% exemption cut-off has been proposed. The delegate also notes that this advice is inconsistent with advice previously given by the ACCS in relation to scheduling fragrance ingredients where there are no strong signals of toxicity at expected use concentrations. The delegate has therefore decided to maintain consistency with previous decisions on fragrance ingredients and to not schedule this substance.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[3];
- Other relevant information.

Public submissions on the interim decision

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

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

Delegate's final decision

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

2.2 Bicyclopyrone

Scheduling proposal

In May 2015 the delegate received a request to consider creating a new entry for a new agricultural chemical, Bicyclopyrone, in Schedule 6 of the SUSMP with a cut-off to Schedule 5 at 20% or less.

Scheduling application

The reasons for the request were:

- An applicant is seeking approval of the new active constituent bicyclopyrone, a member of the 4-hydroxyphenol pyruvate dioxygenase (HPPD)-inhibitor class of herbicides that belongs to the triketone chemical subclass. As a new chemical for AgVet use, it will require consideration by the Delegate/ACCS for SUSMP listing prior to final registration of products containing this active constituent.
- Currently proposed products attached to this application are for agricultural use.

Delegate's reasons for referring this to the committee

While the toxicity profile of bicyclopyrone is reasonably straightforward, there is an issue relating to the interpretation of different findings in rabbit developmental toxicity studies. The OCS evaluation report recommends listing in Schedule 6, with provision for products containing 20% or less to be listed in Schedule 5. As this recommendation may be controversial, the delegate has decided to seek ACCS advice on the scheduling proposal.

The delegate asked the committee the following questions:

- The evaluation process for bicyclopyrone involved a co-operative assessment under the Global Joint Review (GJR) process, with input from the US EPA, Canadian PMRA and OCS. There have been

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

some different interpretations of some of the studies between the three agencies, and the ACCS is asked to comment on the significance of these differences.

- While the acute toxicity profile for bicyclopyrone is consistent with SPF criteria for Schedule 5, or even unscheduled, the toxicological endpoint driving the OCS recommendation for listing in Schedule 6 is the finding of urogenital malformations, (seen from doses as low as 10 mg/kg/day) along with skeletal variations, septal variations of the heart and post-implantation loss from 50 mg/kg/day, and septal defects of the heart (i.e. diverticula or abnormal appearance of the septal wall) at 250 mg/kg/day in a study with Himalayan strain rabbits. These findings were not seen in another development toxicity study using a different strain of rabbits. The ACCS is requested to comment on these findings, and whether it agrees that they (along with any other toxicological findings) support Schedule 6 listing.

Substance summary

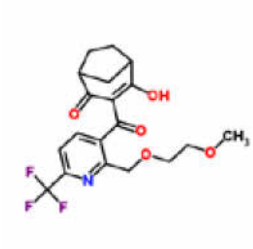

Figure 1: Structure of bicyclopyrone

Acute toxicity

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

Toxicity	Species	Bicyclopyrone	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat (HanRcc:WIST (SPF))	>5000 (no deaths)	Not Scheduled
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat (HanRcc:WIST (SPF))	>5000 (no deaths)	Not Scheduled
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat (HanRcc:WIST (SPF))	>5.2 (no deaths)	Not Scheduled
Skin irritation	Rabbit (NZW)	Non-irritant	Not Scheduled
Eye irritation	Rabbit (NZW)	Slight irritant	Schedule 5
Skin sensitisation (LLNA)	Mouse (CBA/Ca CruBR)	Not sensitising	Not Scheduled

Repeat-dose toxicity

In the rat and dog the primary effect was an increase in plasma tyrosine levels in oral studies in which the levels were measured. Tyrosine levels not being measured in the mouse or rat studies. The available sub-chronic and chronic oral studies indicate that the rat is the most sensitive species to bicyclopyrone toxicity and the mouse the least sensitive, as demonstrated by NOAEL's in chronic studies of 0.72/0.88 mg/kg bw/d in males/females and 233/242 mg/kg bw/d in males/females respectively.

In rats, chronic oral administration of bicyclopyrone resulted in increased kidney weight, chronic progressive nephropathy (males only) and urine clinical chemistry changes as well as thyroid follicular hypertrophy (males only) and corneal opacity and corneal damage (neovascularisation) at 28.4/25.8 mg/kg bw/d in males/females, with decreased body weight and body weight gain seen at higher dose levels. Corneal opacity was also seen following chronic administration of bicyclopyrone in male and female dogs (at 25 mg/kg bw/d) while eye lesions (keratitis or degeneration of corneal epithelium) were seen in male rats (at 250 mg/kg bw/d) in in short-term dermal study.

The influence of bicyclone's MoA, 4-hydroxyphenyl pyruvate dioxygenase (HPPD) inhibition was investigated for the observed eye, thyroid and kidney effects in the rat, the most sensitive species.

Human cases of hereditary diseases that affect tyrosine metabolism indicates that corneal opacity is observed in human with plasma tyrosine concentration of approximately 3000 nmol/ml, and that this level of plasma tyrosine concentration is not expected to occur during occupational use of bicyclopyrone. In support of this, it is reported in the scientific literature that although humans can develop ocular lesions when tyrosine levels are highly elevated for prolonged periods of time, as seen in humans with the rare metabolic disease tyrosinaemia type II (OMIN 276600), the administration of HPPD inhibitors such as the pharmaceutical compound nitisinone given to children and young adults who have the metabolic disease tyrosinaemia type I (OMIN 276700), at doses which are intended to completely inhibit the HPPD enzyme rarely elevates tyrosine sufficiently to cause ocular lesions. Thus, it is clear that humans are significantly less sensitive than rats to elevated tyrosine levels due to HPPD inhibition and, thus, the observed corneal findings in rats (and dogs) following administration of bicyclopyrone are not considered relevant to humans.

It was demonstrated that bicyclopyrone was not an inhibitor of rat thyroid peroxidase activity *in vitro*. Furthermore, the effect of bicyclopyrone on liver and thyroid function was also determined in rats *in vivo* where it was demonstrated that dietary treatment of male rats with bicyclopyrone results in increased tyrosine, decreased T_3 and T_4 (thyroxine), increased thyroid follicular cell hypertrophy and increased liver weight associated with increased hepatocellular centrilobular hypertrophy and increased hepatic UDPGT activity. Thus, for the observed histopathological thyroid fidings there was evidence that bicyclopyrone affected thyroid hormone homeostasis. Further, due to known species differences in thyroid function, due to the plasma half-life of T_4 being shorter in rodents (12 – 24 hours) than in humans (5 – 9 days), there is serum T_4 binding with thyroxine-binding globulin in humans which is absent in rodents (meaning there is more unbound T_4 in rodents susceptible to conjugation and biliary excretion), and constitutive TSH levels are significantly greater in rodents compared to humans (e.g. nearly 25 times greater in rats), rats are considered more susceptible to such thyroid hormone disturbances than humans. In support of this, it is reported in the scientific literature that in the rat free tyrosine can create conditions in the thyroid analogous to mild iodine deficiency, while the HPPD inhibitor nitisinone has been used for the treatment of type I tyrosinaemia since 1991, with some patients therefore taking the drug for >20 years, and during this time there have been no reports of effects on thyroid function. Thus, it is clear that humans are significantly less sensitive than rats to elevated tyrosine levels due to HPPD inhibition and associated thyroid hormone disturbances that can lead to histopathological changes in the thyroid. Thus, the observed thyroid findings in rats following administration of bicyclopyrone are not considered relevant to humans.

While the applicant proposed that the observed chronic progressive nephropathy associated with prolonged administration of bicyclopyrone to rats is due to elevated tyrosine following HPPD inhibition and are not relevant to man, the OCS does not consider that the limited data and evaluation presented establish that the observed chronic progressive nephropathy definitively occurred (solely) by HPPD inhibition and increased tyrosine levels. Consequently, OCS considers that this kidney finding in male rats is likely relevant to humans.

The observed systemic toxicity occurred at dose levels and exposure duration sufficiently far from the expected exposures associated with use patterns that they would not be consistent with SPF guidance on scheduling.

Mutagenicity/Genotoxicity

Bicyclopyrone was not mutagenic or clastogenic *in vitro* with and without metabolic activation, and in vivo was not clastogenic in rat bone marrow cells and did not induce DNA repair (indicative of DNA damage) in rat liver cells. Thus, the available data indicate bicyclopyrone is not an *in vivo* genotoxicant. Scheduling is not required for this human health endpoint.

Carcinogenicity

In an 80 week carcinogenicity study in mice, a slight increase in the incidence of bronchiole-alveolar adenoma in the lung above the laboratory historical control range (36%, HC 24 – 30%), was seen near the limit dose of 1000 mg/kg bw/d (i.e. 940 mg/kg bw/d) in the absence of treatment related non-neoplastic change in the lung or bronchio-alveolar carcinoma. Additionally, this dose level exceeded the maximum tolerated dose (MTD) as shown by body weight gain being decreased for the duration of the study (↓13% to ↓29%). Thus, this benign tumour finding in males does not provide robust and reliable evidence of a carcinogenic potential. No increased incidence of tumour findings was seen in female mice.

In the 104-week carcinogenicity phase of a dietary study in male rats, at 500, 2500 and 5000 ppm (equivalent to 0.28, 141 and 280 mg/kg bw/d) a slight increase was seen in squamous cell papilloma of the cornea was seen in 2 males (4% animals) at each dose level along with squamous cell carcinoma of the cornea in 1, 1 and 3 males (2%, 2% and 6% of animals) respectively that was not statistically significant but was absent in control animals. These findings were seen in the presence of ocular opacity, keratitis and regenerative hyperplasia of the cornea, and as discussed above under 'Repeat dose toxicity', rats are significantly more sensitive to the effects of HDDP inhibitors than humans, and that the ocular keratitis and regenerative hyperplasia observed in rats is directly linked to the resulting highly elevated plasma tyrosine. Furthermore, the progression of ocular keratitis and regenerative hyperplasia in the rat cornea to corneal cell tumours at high levels of tyrosine, while not directly demonstrated, may further suggest a role of tyrosine and not bicyclopyrone in the development of these tumours. Consequently, overall, it is considered that the observed low incidences of corneal cell tumours in male rats only are unlikely to be relevant to humans. No increased incidence of tumour findings was seen in female rats.

Therefore, it is considered that no tumours relevant to humans were seen in male and female rats and mice, and therefore scheduling is not required for this human health endpoint.

Reproduction and developmental toxicity

Similar to findings in repeat dose studies, in a 2-generation dietary study in rats ocular effects including corneal opacity and vascular keratitis were seen in parental animals with decreased body weight and body weight gain also seen at higher dose levels. Ocular effects (corneal opacity, corneal roughness and vascular keratitis) and decreased bodyweight and bodyweight gain were also seen in offspring, in the presence of parental toxicity. In F1 parental males only, a significant increase in the number of abnormal sperm and a decrease in sperm velocities was seen at high dose levels in the presence of general toxicity (decreased body weight) in the absence of an effect on reproductivity. Consequently, bicyclopyrone is not considered a reproductive toxicant. Scheduling is not required for this human health endpoint.

Developmental toxicity studies on bicyclopyrone were performed in Wistar rats and in two species of rabbit, the New Zealand White and Himalayan, whose dose levels were determined from developmental dose-range finding studies.

In rats, skeletal variations (increased incidence of full or rudimentary supernumerary ribs, pelvic girdle malposition and long costal cartilage 11) were observed in the presence of maternal toxicity at doses of 100 mg/kg bw/d, the lowest dose tested. The skeletal variations while treatment related were considered a secondary non-specific consequence of the observed marked maternal toxicity (i.e. a corrected body weight gain decrease of 11% at GD 21, with decreases in body weight gain of 15 – 83% from GD 6 – 11). Thus, bicyclopyrone was not considered a developmental toxicant in rats.

In New Zealand White rabbits, evidence of foetotoxicity included an increased incidence of two skeletal variations (13th full rib, 27th pre-sacral vertebrae) in the absence of maternal toxicity at 10 mg/kg bw/d. While these increases in the 13th full rib (57.2% per litter) and 27th pre-sacral vertebrae (27.2% per litter) were outside of the upper laboratory historical control range (45.7% and 15.5% per litter respectively) and are treatment related OCS considers that the change in the incidence of these common variants (as demonstrated by the incidence seen in the historical control database) alone do not warrant classification as a hazard for developmental toxicity. Furthermore, it was noted that no additional skeletal findings, or visceral findings, were seen at increased dose levels in the presence of severe maternal toxicity (i.e. at a dose level producing mortality/moribundity in does). Thus, bicyclopyrone was not considered a developmental toxicant in NZW rabbits.

Two studies were available in Himalayan rabbits, one with dose levels of 0, 10, 50 and 250 mg/kg bw/d (study 1) and the other with dose levels of 0, 1, 10 and 250 mg/kg bw/d (study 2). Taking the findings together allowed a more informed view of potential spontaneous rates in foetuses and a more comprehensive dose response for maternal and foetal findings to be established.

In study 1, the maternal NOAEL was established at 50 mg/kg bw/d based on macroscopic findings in the stomach wall of females and a sustained absence in body weight gain (i.e. daily decreases of -1.51 to -8.12 g) from GD 7 – 13 at 250 mg/kg bw/day the highest dose tested. At 10 mg/kg bw/d the lowest dose tested, and in the absence of maternal toxicity, an increased incidence was seen in urogenital malformations (in 2% of foetuses, 14% of foetuses) that were absent in control animals from both studies along with skeletal variations. Also in the absence of maternal toxicity, at 50 mg/kg bw/d a treatment related and toxicologically significant increase was seen in septal variations of the heart (in 20% foetuses and 53% litters, with a highest incidence of 16% and 68% respectively seen in study 2) and in post-implantation loss (20.3% of implantation sites with a mean of per litter of 1.4, compared to upper historical control values of 15.9% and 1.2 respectively).

In study 2, the maternal NOAEL was established at 10 mg/kg bw/d based on two mortalities and signs clinical signs of toxicity along with signs of stomach irritation in two does at 250 mg/kg/d. At 10 mg/kg bw/d in the absence of maternal toxicity, and consistent with the findings in study 1 at the same dose level, urogenital malformation were seen (in 2% of foetuses and 5% of litters) along with skeletal variations.

Therefore, taking the findings from the two developmental studies in Himalayan rabbits together, it is considered that urogenital malformations were seen from 10 mg/kg/day along with skeletal variations, septal variations of the heart and post-implantaion loss from 50 mg/kg/day, and septal defects of the heart (i.e. deverticula or abnormal appearance of the septal wall) at 250 mg/kg/day in this study. Maternal toxicity was seen from 50 mg/kg bw/d, so the urogenital malformations and skeletal findings at 10 mg/kg bw/d were seen in the absence of maternal toxicity, while OCS considers that the observed septal variations and defects along with post-implantation loss seen in the presence of maternal toxicity were unlikely to be a secondary non-specific consequence of such (i.e. are considered evidence of a developmental toxicity potential). Thus, bicyclopyrone was considered to be a developmental toxicant in Himalayan rabbits and scheduling is required for this human health endpoint.

However, while skeletal findings were seen in Wistar rats and NZW rabbits (a secondary non-specific consequence of maternal toxicity in rats) bicyclopyrone was not considered to be a developmental toxicant in this species/strain. Thus, while the findings in one species do not warrant Schedule 7, although bicyclopyrone was only considered a developmental toxicant in one of two rabbit strains, Schedule 6 is considered more appropriate than Schedule 5 due to the nature of the observed foetal findings; visceral changes (urogenital malformations and septal variations in the heart) and post-implantation loss.

Other toxicology endpoints

Bicyclopyrone was not a neurotoxicant in male and female rats in an acute oral neurotoxicity study up to and including the limit dose (2000 mg/kg bw). In a subchronic dietary study, decreases in mean brain weight were seen in males only at 4 (8%), 35 (8%) and 336 (11%) mg/kg bw/d that were

considered to be due to a high mean value in control males (2.38 g) when compared to the historical control range means (2.2 and 2.0 g from two studies), and it was noted that with the exception of 1 male in the 500 ppm dose group all brain weights in males at 50 and 500 ppm were within the historical control range (1.96 – 2.29 g). While at 5000 ppm, the brain weight in only 2 of the 5 males was lower than the minimum historical control value. Therefore, and noting an absence of an effect on functional parameters or histopathological changes to the brain, this finding in one sex is not considered to demonstrate an adverse effect and bicyclopyrone is not considered to be a neurotoxicant. Scheduling is not required for this human health endpoint.

Bicyclopyrone was not immunotoxic in female mice. Scheduling is not required for this human health endpoint.

Observation in humans

No information was provided.

Public exposure

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

International regulations

Bicyclopyrone has been approved for use by Canada PMRA for agricultural use Canada PMRA publication.

Scheduling status

Bicyclopyrone is not currently specifically scheduled.

Scheduling history

Bicyclopyrone has not been previously considered for scheduling; no scheduling history is available.

Public pre-meeting submissions

Two public submissions were received. One submission agreed with the OCS assessment that in the studies assessed the skeletal variations, urogenital malformations and presence of significant maternal toxicity that occurred are not a dose-dependent effect of bicyclopyrone. The other provided comment on the OCS report to which the OCS replied by highlighting that the public submission did not take into account other abnormalities that occurred in the studies assessed.

The OCS considers the post-implantation loss and septal variations and defects of the heart at 250mg/kilo bw/d to be significant issues and are dose-dependent and therefore toxicologically significant. The OCS maintained their recommendation.

The public submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The Committee recommended a new Schedule 6 entry be created for bicyclopyrone except when in Schedule 5, for when preparations contain 20% or less of bicyclopyrone.

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Foetoxicity or potential for developmental toxicity consistent with Schedule 6.

Delegate's interim decision

Schedule 6—New Entry

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

Schedule 5—New Entry

BICYCLOPYRONE in preparations containing 20 per cent or less of bicyclopyrone.

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

The proposed implementation date is 1 February 2016. An early implementation date is proposed to facilitate clearance of the active ingredient by the APVMA and prior to registration of a product containing bicyclopyrone.

The reasons for the interim decision comprised the following:

> The toxicological profile of bicyclopyrone is well characterised in the OCS evaluation report. While the low acute and chronic toxicity profile suggests that scheduling is not necessary, the developmental and fetotoxicity potential of bicyclopyrone suggest that it should be listed in Schedule 6, even though this toxicity is not consistent across relevant tests in different species and strains. The delegate notes that this is consistent with the advice provided by the ACCS. The delegate also accepts ACCS advice that the dose-related nature of the developmental toxicity allows for a product containing 20% or less of bicyclopyrone to be down-scheduled to Schedule 5, with adequate Margin of Exposure (MoE) estimates associated with its proposed uses. The delegate also notes ACCS comment that findings of unilateral kidney loss in some dams in the Himalayan rabbit study suggests a hereditary response, rather than a response related to bicyclopyrone. Since the OCS report drew attention to some developmental toxicity other than the urogenital effects, the delegate affirms that the Schedule 6 listing for bicyclopyrone remains appropriate.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

One submission was received. The submission referred to the toxicity studies that were assessed in the OCS Health Report and wished to draw specific attention to the cardiac defects and post-implantation loss in Himalayan rabbits. The conclusions in the submission were that the toxicity issues related to the noted defects in Himalayan rabbits were restricted to the highest dose (250 mg/kg), whereas the observed defects in the lower doses were only incidental.

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

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

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as the information received does not overcome the reasons behind the interim decision. The delegate notes that the submission primarily addresses the cardiovascular defects and implantation losses noted in both studies in the Himalayan rabbit, and argues that the effects are only of significance at the highest dose, where there was evidence of maternal toxicity. However, there is some evidence that the dose-response may not be confined to only the highest dose, and the finding of such lesions in the heart that are possibly dose-related adds weight to the ACCS advice that Schedule 6 is a more appropriate listing, with an exemption to Schedule 5 at 20% based on estimates of the margin of exposure.

The delegate has confirmed that the reasons for the final decision are therefore in keeping with those for the interim decision.

2.3 *Clitoria ternatea* extract

Scheduling proposal

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

- In June 2015 the delegate received a request to consider new entry for *Clitoria ternatea* extract in Schedule 5, based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to approve a new biological active constituent.

Scheduling application

The reasons for the request were:

- *Clitoria ternatea* extract is a new plant-based ethanolic extract comprised of a number of chemicals and plant based compounds including flavonoid glycosides, essential amino acids, pigments, cyclic peptides, lipids, mineral salts and carbohydrates. It is intended for use in an agricultural product.
- The skin sensitisation study (by local lymph node assay) did not provide robust evidence of a skin sensitisation potential.
- No acute inhalational toxicity testing was undertaken, however based on the physical properties of the extract and the low toxicity findings in other studies; the OCS does not consider *Clitoria ternatea* extract to have inhalational safety concerns at this time.
- No eye irritation studies were undertaken. However, based on the residual ethanol within the extract and the potential mechanical irritation of the extract; *Clitoria ternatea* extract is considered to have a moderate eye irritation potential.
- The systemic findings in short-term studies were not considered to warrant scheduling.
- *Clitoria ternatea* extract was not an *in vivo* or *in vitro* genotoxicant.
- The carcinogenicity or immunotoxicity potential of *Clitoria ternatea* extract cannot be determined at this time.

Delegate's reasons for referring this to the committee

While the OCS evaluation report is clear on the basis for its recommendation to list *Clitoria ternatea* extract in Schedule 5, the sponsor has requested listing in Appendix B (i.e. not scheduled). The SUSMP is quite explicit that a sponsor application to create an Appendix B entry will not be accepted. In order to resolve the differences between the sponsor and the OCS as to the most appropriate scheduling action, the delegate seeks advice from the ACCS.

The delegate asked the committee the following questions:

- The OCS report indicates that the toxicological endpoint demonstrating consistency with SPF criteria for listing in Schedule 5, is the presumed eye irritancy associated with instilling a powdered substance containing traces of ethanol in the eye. Other toxicological endpoints suggest that scheduling is not necessary. Does the ACCS support the OCS recommendation for listing in Schedule 5?
- Does the ACCS agree that the lack of an acute inhalation toxicity study is not critical, given the OCS assessment of the matter and the sponsor contention that the potential for the product to generate an aerosol makes it unlikely that it would pose an inhalational hazard and the physico-chemical properties of the extract did not enable the appropriate environment for inhalational studies in the rat.

Substance summary

Toxicokinetics/ADME

Clitoria ternatea extract consists of a range of plant based compounds including flavonoid glycosides, essential amino acids, pigments, cyclic peptides, lipids, mineral salts and carbohydrates common to legumes; all of which are likely to have different absorption, distribution, metabolism and excretion properties. No single or group of ingredients within the extract was identified as a cause of local or systemic toxicity.

Acute toxicity

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

Toxicity	Species	*Clitoria ternatea* extract	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} >2000 mg/kg bw	
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} >2000 mg/kg bw	
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	Not considered to pose a hazard at this time	
Skin irritation	Rabbits	Non-irritating	Appendix B
Eye irritation	N/A	Presumed slight-moderate	Schedule 5
Skin sensitisation LLNA	Mice	Non-sensitiser	

Repeat-dose toxicity

No toxicological effects or microscopic examination abnormalities were noted in repeat dose oral and dermal studies.

Reproduction and developmental toxicity

No information was provided. However, OCS notes that no toxicity related effects were noted on reproductive organs in repeat-dose studies.

Neurotoxicity

No information was provided. However, OCS notes that no neurotoxic effects were noted in acute or repeat dose studies.

Genotoxicity

Clitoria ternatea extract tested negative in in vivo and in vitro genotoxicity studies.

Observation in humans

No information was provided.

Public exposure

No information was provided.

No domestic (general public) exposure is expected for *Clitoria ternatea* extract at the time of this application. The intended use of *Clitoria ternatea* extract is as an insecticide on crops. The OCS notes that the *Clitoria ternatea* plant is already used in Australia in homeopathic remedies and teas and as fodder for cattle.

International regulations

No information was provided.

Scheduling status

Clitoria ternatea extract is not specifically scheduled. There is little or no precedent for including a plant extract in the Schedules, although there are several powdered or granulated microbiological extracts with comparable toxicity profile (eye irritancy) that have resulted in them being listed in either Schedule 5 or Appendix B. There is one insecticidal plant extract (*Azadirachta indica* extract), that is currently listed in Schedules 5, 6 and 10. However, its toxicological profile is distinctly different, with potential reproductive toxicity as the critical toxicological endpoint driving the scheduling.

Scheduling history

As *Clitoria ternatea* extract is not currently specifically scheduled, scheduling history is not available.

Public pre-meeting submissions

One public submission was received. The submission stated that there was confusion over why the substance is being proposed for scheduling. The confusion stemmed from the substance not being regulated in other areas, such as its approval for use in food in Australia and that there are no restrictions in place for its use in cosmetics in the US or EU.

The public submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended *Clitoria ternatea* extract be listed in Appendix B.

Appendix B, Part 1 – Reasons for entry

Substance	Standard Statement
Clitoria ternatea extract	B – use pattern restricts hazard and area of use

Appendix B, Part 2 – areas of use

Substance	Standard Statement
Clitoria ternatea extract	1.2 – Insecticide

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Low toxicity for the proposed use pattern

Delegate's interim decision

Appendix B—New Entry

CLITORIA TERNATEA EXTRACT

Subject to: (a) low toxicity; 1.2: insecticide.

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

The proposed implementation date is 1 February 2016.

The reasons for the interim decision comprised the following:

> The toxicological profile of *Clitoria ternatea* extract is well characterised in the OCS evaluation report. The low acute and chronic toxicity profile suggests that scheduling is not necessary. While the acute toxicity tests are consistent with SPF criterial for listing in Schedule 5, the fact that the highest doses tested were at the lower end of the range does not preclude the likelihood that toxic doses are higher than the range specified in SPF Schedule 5 criteria. Accordingly, the delegate accepts ACCS advice that *Clitoria ternatea* extract is sufficiently nontoxic to be listed in Appendix B.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

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

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

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

Delegate's final decision

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

2.4 Cyclopentane, alpha,alpha-dimethylpropanol

Scheduling proposal

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

- In April 2015 the delegate received a request to consider creating a new entry for cyclopentanepropanol, alpha,alpha-dimethyl- in Schedule 6 when used in cosmetic and household products, with appropriate concentration cut-offs to exempt from scheduling for preparations with low concentrations.

Scheduling application

The reasons for the request were:

- The chemical is an eye irritant, consistent with the Schedule 6 factors and skin irritant, consistent with Schedule 5 factors.
- The NICNAS recommended usage concentrations of 1% in fine fragrances, 0.5% in other cosmetic products and 1% in household products correspond to the maximum proposed usage concentrations by the notifier. The NICNAS assessment determined that there was no unreasonable risk to the public when used at these concentrations.
- A margin of exposure (MoE) value of ≥ 100 was considered acceptable to account for intra- and inter-species differences. Using an NOAEL of 300 mg/kg bw/day, which was derived from a 28-day, oral repeat dose toxicity study in rats and an estimated exposure value of 1.756 mg/kg bw/day from use of the chemical in cosmetic and household products, a MoE of 171 was estimated.
- The chemical has been early listed on to the Australian Inventory of Chemical Substances (AICS) at the request of the notifier and is therefore currently available for use by introducers other than the original notifier.

Delegate's reasons for referring this to the committee

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

The delegate asked the committee the following questions:

- Does the ACCS consider that the toxicological profile of cyclopentanepropanol, α,α-dimethyl- is sufficiently similar to the seven fragrance chemicals where no scheduling action was recommended, or is it more like 4,4-dimethyl-1-cyclohexene-1 propanal, where listing in Schedule 6 was recommended, along with different product-related exemption cut-offs?

- If scheduling is recommended, is the chemical name cyclopentanepropanol, alpha,alpha-dimethyl- the preferred name for listing (or some other name)?
- Does the ACCS support different exempt cut-offs for a Schedule 6 entry for different product types, as proposed in the NICNAS report?

Substance summary

Please refer to the New Chemical assessment report for cyclopentanepropanol, alpha,alpha-dimethyl. This report is publicly available on the NICNAS website: NICNAS report.

Acute toxicity

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

Toxicity	Species	Cyclopentanepropanol, alpha,alpha-dimethyl-	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2,000	None
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2,000	None
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Not provided	Not provided	-
Skin irritation	Rabbit	Slight irritant	Consistent with Schedule 5
Eye irritation	Rabbit	Irritant	Consistent with Schedule 6
Skin sensitisation (Local lymph node assay)	Mouse	No evidence of sensitisation	None

Repeat dose toxicity

A 28-day repeat dose study by oral gavage was conducted in rats with the notified chemical at dose levels of 30, 300 and 1000 mg/kg/day. Changes in liver weights and body weight gain along with histopathological findings in the high dose group were considered to be adverse and hence the lower dose of 300 mg/kg bw/day was chosen as the No Observed Adverse Effect Level (NOAEL) for systemic toxicity.

Mutagenicity

The chemical was not mutagenic in a bacterial reverse mutation assay.

Genotoxicity

The chemical was not clastogenic in an in vitro mammalian chromosome aberration test.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

There will be diffuse and repeated exposure of the public to the chemical (at ≤ 1% concentration) through the widespread use of household products and both rinse-off and leave-on cosmetic products. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

International regulations

No information was provided.

Scheduling status

Cyclopentanepropanol, alpha,alpha-dimethyl- is not specifically scheduled.

Scheduling history

Cyclopentanepropanol, alpha,alpha-dimethyl- has not been previously considered for scheduling; therefore, scheduling history is not available. However, for the one fragrance ingredient where the ACCS did recommend scheduling (see delegates reasons for referral below), the wording used in the listing was:

Schedule 6 – New Entry

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

a) in leave-on cosmetic preparations containing 0.1 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal;

b) in rinse-off cosmetic preparations containing 0.5 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal; or

c) in other preparations containing 1 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal.

Public pre-meeting submissions

No public submission was received.

Summary of ACCS advice to the delegate

The committee recommended a new Schedule 5 entry be created for cyclopentanepropanol, alpha,alpha-dimethyl- except in preparations containing 1% or less.

The committee also recommended changing the name from its original reference of cyclopentane, alpha,alpha-dimethylpropanol is CYCLOPENTANEPROPANOL, ALPHA,ALPHA-DIMETHYL-

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

· Meets the criteria for Schedule 5 as an eye irritant.

Delegate's interim decision

The delegate has decided not to accept ACCS advice on this matter. The delegate has decided not to schedule cyclopentanepropanol, alpha,alpha-dimethyl-.

The reasons for the interim decision comprised the following:

> The delegate notes that the ACCS advice to include this fragrance ingredient in Schedule 5 is based primarily on the fact that its acute toxicity and skin/eye irritancy potential is consistent with SPF criteria for listing in Schedule 5, and that a 1% exemption cut-off has been proposed. The delegate also notes that this advice is inconsistent with advice previously given by the ACCS in relation to scheduling fragrance ingredients where there are no strong signals of toxicity at expected use concentrations. The delegate has therefore decided to maintain consistency with previous decisions on fragrance ingredients and not to schedule this substance.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

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

2.5 Hydramethylnon

Scheduling proposal

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

- the delegate received a request to consider amending the current Schedule 5 entry for hydramethylnon to include a concentration cut-off exemption at 0.365% w/w.

Scheduling application

In March 2014, the applicant, as part of an application to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to extend the usage of a currently registered product (professional use), requested that the delegate consider amending the current Schedule 5 entry for hydramethylnon to allow for the inclusion of a product containing 0.365% w/w hydramethylnon.

The OCS performed a risk assessment for the professional use of the product in August 2013. The extension of use to include the domestic user was considered as part of the risk assessment provided

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

to APVMA on 4 December 2014. The OCS considers that the uncertainty regarding reproductive toxicity is sufficient to retain the schedule 6 entry, particularly for professional users.

In considering the available information, the OCS considers that the professional use pattern for the product is consistent with a Schedule 6 entry. This recommendation is based on the potential for long term use of hydramethylnon, which may result in delayed onset of irreversible effects to male fertility at low doses. Recommendations for appropriate label statements have been made for the application of the product via aerial and hand –held spreaders, however, the risk to workers arising from hand dispersal of bait could not be sufficiently mitigated through the use of PPE. Whilst the acute toxicity profile is consistent with a Schedule 5 entry and the risk for the domestic user of the product is considered acceptable (i.e. MOE > 100), the uncertainty regarding the potential for harm arising from an accidental poisoning scenario is considered sufficient to retain the Schedule 6 entry for the domestic market.

The reasons for the request were:

- The product has low acute toxicity via oral and dermal exposure and does not cause skin irritation or sensitization which is consistent with Schedule 5.

Delegate's reasons for referring this to the committee

This is a re-scheduling proposal for a substance previously considered by the NDPSC and currently listed in Schedules 5 and 6. Since there is disagreement between the recommendations of the OCS evaluation report, and the applicant's response, the delegate requested advice from the ACCS.

The delegate asked the committee the following questions:

- The key issue considered by the NDPSC in 1996 was whether a brief exposure to a granular bait containing hydramethlynon represented a risk of testicular toxicity to a child ingesting a small amount of the bait. The DPSC in 1990 had apparently been satisfied that it was unlikely a child could access a sufficient dose of hydramethylnon when contained in a plastic labyrinth bait station, and it allowed a down-scheduling for such a product to Schedule 5. Pyriproxyfen, the other active ingredient of the granular ant bait under consideration in this proposal has low toxicity, and was included in Appendix B at the August 1994 NDPSC meeting.

- Testicular atrophy and resultant infertility appear to be the main reasons behind listing hydramethylnon in Schedule 6, because other aspects of its toxicity are more consistent with listing in Schedule 5. The OCS evaluation report on a current product submission (granular ant bait in a shaker pack for domestic use and a different pack for professional use) notes that no specific toxicity study has been provided to address the testicular toxicity concerns raised by the NDPSC. The sponsor has argued that the likely exposure pattern for a child ingesting enough of the granular product is negligible, and that in a single dose experiment in rats, impaired fertility was not seen after a dose of 800 mg/kg (OCS noted that this was assessed 3 weeks after the exposure). Which argument does the ACCS support in relation to the testicular toxicity potential?

- Does the OCS evaluation report provide any information on the Mode of Action (MoA) for the testicular toxicity, and if not, how critical is this lack of information?

- Do the differences in the proposed use patterns (frequency of application and method of application) justify having a product with identical actives and toxicological profile in Schedule 6 for professional use, and in Schedule 5 for domestic use? If so, does the wording of the Schedule 5 sub-clause adequately differentiate the domestic product shaker pack from the professional product?

- Is the wording of the proposed specification of the 'shaker pack for domestic use containing 500g or less of the granular material' consistent with wording used in the SUSMP and consistent with enforcement by State/Territory law?

Substance summary

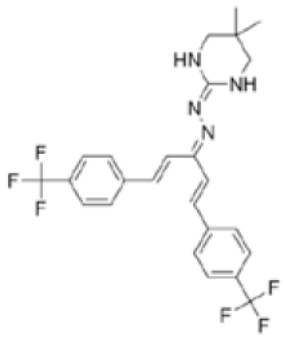

Figure 1: Molecular structure of hydramethylnon (CAS: 67485-29-4): tetrahydro-5,5-dimethyl-2(1H)-pyrimidinone(3-(4-(trifluoromethyl)phenyl)-1-(2-(4-(trifluoromethyl)phenyl)ethenyl)-2-propenylidene)hydrazone

Acute toxicity

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

Toxicity	Species	Hydramethylnon	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	Low (LD_{50}=1131 mg/kg bw)	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	Low (LD_{50}>15 g/kg bw)	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	Low (LC_{50}>600 mg/m^3 no deaths)	Schedule 6
Skin irritation	Rabbit	Slight	
Eye irritation	Rabbit	Moderate	
Skin sensitisation (Local lymph node assay)	Guinea pig	Non-sensitiser	

The acute toxicity of the product forming the basis for the down scheduling consideration at 0.365 % w/w hydramethylnon (plus 0.250 % w/w pyriproxyfen) is included in the table below.

Toxicity end point	Hydramethylnon	Pyriproxyfen	Synergy Ant Bait
Oral (mg/kg bw)	Low (LD_{50}=1131 mg/kg bd/w)	Low (LD_{50}>5000 mg/kg bd/w)	Low (LD_{50}>2000 mg/kg bd/w no deaths)
Dermal (mg/kg bw)	Low (LD_{50}>15 g/kg bd/w)	Low (LD_{50}>2000 mg/kg bd/w)	Low (LD_{50}>2000 mg/kg bd/w no deaths)

Toxicity end point	Hydramethylnon	Pyriproxyfen	Synergy Ant Bait
Inhalational (mg/m^3)	Low (LC_{50}>600 mg/m^3 no deaths)	Low (LC_{50}>1300 mg/m^3)	Low *
Skin irritation	Slight	Nil	Non irritant
Eye irritation	Moderate	Slight	Non-irritant*
Skin sensitisation	Nil	Nil	Non sensitiser

*product toxicity was estimated from available information on product ingredients

Repeat dose toxicity

In a 3-week dermal toxicity study, New Zealand White rabbits (10/sex/dose) were administered 0, 10, 50, or 250 mg/kg bw hydramethylnon on abraded or unabraded skin for 6 hours/day, 5 days/week for 3 weeks. The vehicle was not stated. Clinical signs of systemic toxicity were not observed in any group during the treatment. Food consumption and body weight gains were reduced in the high dose groups only. High dose females presented with significantly reduced platelet counts at termination. High dose group animals also showed reduced relative liver and brain weights, but these changes were probably related to the lower body weights. The dermal irritation was of similar severity in all groups when compared to controls, indicating an irritant vehicle rather than a test material-related effect. The NOEL for systemic toxicity following dermal application was 50 mg/kg bw/d, based on reduced appetite, reduced body weight and reduced platelet counts observed at the next highest dose.

In a 28-day feeding study, CD rats, (3/sex/dose) received 0, 50, 100, 200, 400 or 800 ppm hydramethylnon in their diet. The 800 ppm group was killed moribund at the end of the second week. Anorexia and significant reduction of food consumption occurred in the three highest dose groups. Depressed weight gain and decreased relative weight of a number of organs was observed at the 400 and 800 ppm level. Gross pathology was unremarkable; histopathological examination revealed focal tubular degeneration of testes in the group of 200, 400 and 800 ppm. The NOEL was 100 ppm (approximately 5 mg/kg bw/d) based on anorexia, decreased food consumption, reduced weight gain and testicular atrophy seen at 200 ppm and above.

In another 28-day feeding study, CD rats (6/sex/dose) were given 0, 25, 50, 75, or 100 ppm hydramethylnon in diet. No mortalities or clinical signs of toxicity were noted. A slight decrease in food consumption was noted in the 100 ppm group, accompanied by depressed weight gain in females during the first half of the study. Haematological values remained within the normal range in all groups. The NOEL was 75 ppm (approximately 3.75 mg/kg bw/d) based on the reduced weight gain and food consumption in the 100 ppm group.

In a 91-day feeding study, CD rats (20/sex/dose) were given 0, 25, 50, 100 or 200 ppm hydramethylnon. No mortality occurred during the treatment period. Decreased food intakes were observed in high dose males during all treatment weeks except weeks 9, 10 and 13. Decreased food intake was also noted in females during the first 3 weeks. A significant decrease in body weights of high dose rats of both sexes occurred throughout the study. Clinical chemistry, haematological parameters and urinalysis were unaffected by treatment. No organ weight changes were noted with the exception of decreased absolute and relative testicular weights in high dose animals, accompanied by testicular atrophy at ≥100 ppm. The NOEL was 50 ppm (approximately 2.5 mg/kg bw/d) based on testicular lesions at 100 ppm and above.

In a 91-day oral study, beagle dogs (4/sex/dose) received 0, 3, 6 or 12 mg/kg bw/d hydramethylnon in gelatin capsules. Middle and high dose dogs began to refuse food from second week of the experiment; all high dose dogs were sacrificed moribund by day 53 and only one male and one female

dog at 6 mg/kg bw/d survived through to study termination. The mean body weight gains were depressed in the middle and high dose groups probably as a result of appetite loss. These dogs exhibited intermittent episodes of tremors and short episodes of convulsions, with occasional vomiting. Liver weights of low dose males as well as the liver/body weight ratio were increased, however, no abnormal hepatic histopathology was found in low dose animals. Gross pathology indicated cachexia in all middle and high dose dogs accompanied by wasting of muscle and subcutaneous fat and also accompanied by testicular atrophy in the middle and high dose dogs. No NOEL was established in this study.

In a 26-week sub-chronic toxicity study, beagle dogs (4/sex/group) were administered 0, 0.33, 1.0, or 3.0 mg/kg bw hydramethylnon by oral capsule. No deaths were observed. Clinical signs of toxicity consisted of a dose-related increased incidence of soft and mucoid stools and diarrhoea in all treated groups. Treatment-related changes in organ weights included a dose-related increase in the liver weights, liver/body weight ratios and liver/brain weight ratios in the middle and high-dose males and females (except the liver/brain ratio in the high dose females). Gross necropsy finding indicated only a yellow-coloured body fat in 4/8 high dose dogs. The NOEL in this study was 1 mg/kg bw/d based on the toxicity at 3.0 mg/kg bw/d consisting of reduced body weights and anorexia in one animal.

In an 18-month chronic toxicity study, CD mice (50/sex/dose) were given 0, 25, 50, 100 or 200 ppm hydramethylnon in the diet. A dose-related increase in mortality over the course of the study was seen, with clear indications of treatment-related mortality evident by week 26 of the study. Mean body weights were reduced in the two highest dose groups. Food consumption was decreased in the highest dose group only after 12 weeks. Histological examination indicated major lesions in the testes of males at 50, 100 or 200 ppm. The dose-related lesions consisted of hypospermia, interstitial cell hyperplasia of Leidig cells and germinal cell degeneration. Other lesions included an increased incidence of pigment-laden macrophages in alveolar spaces of the lung at 200 ppm group and an increased incidence and severity of pigment accumulation in the cytoplasm of cortical renal tubules among 200 ppm females. An increased incidence of renal amyloidosis was observed in males administered 100 and 200 ppm hydramethylnon and females administered 50, 100 and 200 ppm hydramethylnon. The amyloidosis was bilateral, with a glomerular distribution in mild cases and glomerular and tubular involvement in the more severe lesions. No increase in tumours was detected in the study. The NOEL in this study was 25 ppm (3.75 mg/kg bw/d) based on the testicular atrophy and renal amyloidosis observed at 50 ppm and above.

In a 2-year chronic toxicity study, CD rats (50/sex/dose) received 0, 25, 50, 100 or 200 ppm hydramethylnon in the diet. No clinical signs were observed during the study. Food consumption was decreased in the high dose group (both sexes) and mean body weights were reduced in high dose animals (both sexes) and middle-dose females. Clinical pathology was unaffected by treatment. A statistically significant decrease was observed in absolute and relative testes weight (% brain) in the two highest male dose groups, and a decrease in the relative weight (% body) for the highest dose group. These testes weight changes correlated with small and soft testes at gross necropsy examination, and a significant increase in the incidence of bilateral testicular atrophy characterised by almost complete loss of germinal cell and, arteritis tissue in histopathological examination. Increased absolute and relative heart weights in the two highest dose groups was also observed (without histopathological correlates), and an increased absolute and relative kidney weight in ≥50 ppm males and ≥100 ppm females. Glomerulonephrosis was increased in the highest dose group. Hydramethylnon was not oncogenic at any dose tested after evaluation. The NOEL for this study was 50 ppm (2.5 mg/kg bw/d) based on the toxic effects consisting of reduced food consumption and body weight gain and increased incidence of testicular atrophy and exacerbated glomerulonephritis at 100 ppm and above.

Genotoxicity

Hydramethylnon was negative in the Ames test.

Hydramethylnon caused infertility in male rats, due to aspermia, in a dominant lethal test when administered at doses of 30 or 90 mg/kg bw/d for 5 days. At 30 mg/kg bw/d infertility was reversed in all animals at 12 weeks after dosing, while partial reversal of infertility was noted at 90 mg/kg bw/d

after 17 weeks in 5/10 animals, with remaining 90 mg/kg bw/d males noted as infertile. Treatment with the compound had no effect on implantation parameters in females.

Hydramethylnon did not induce chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of metabolic activation.

Carcinogenicity

There was no evidence of treatment related carcinogenicity in long term repeat dose studies with rats and mice.

Reproduction and developmental toxicity

In a 3-generation reproduction study, CD rats were given hydramethylnon for 3 successive generations at 0, 25, 50, 100 or 200 ppm. No treatment-related deaths occurred in the adult generations. Mean body weight gains of males at 100 or 200 ppm and females at 50, 100 or 200 ppm were significantly reduced in the growth period. While offspring generations (F_1 onwards) were not retained at ≥100 ppm due to lack of offspring, the subsequent F_1 and F_2 generations at 25 and 50 ppm showed normal weight gain and food consumption during the growth phase. The reproductive performance at the two highest dose levels in the F_0 generation was markedly reduced. At 100 ppm, mating indices were higher than controls during both mating periods, however, none of the females delivered an F_{1a} litter and only 6 females delivered an F_{1b} litter. Litters of these females contained fewer pups and some oedematous pups. At 200 ppm, mating indices were generally lower than controls for both mating intervals and none of the females delivered litters. The reduced fertility in the F_0 group at 100 or 200 ppm was accompanied by increased incidence of small testes in these groups from week 19, tubular degenerative changes and aspermia, with 200 ppm males also presenting with mineralisation of a few degenerated tubules. The NOEL was 50 ppm (2.5 mg/kg bw/d) based on reduced fertility at ≥100 ppm.

In a 2-generation reproduction study, CD rats received hydramethylnon at 0, 25, 50 and 75 ppm in the diet. Reduced body weight gains during the 10 week premating period and a transient reduction in food consumption in the first 3-4 weeks of dosing were recorded in F_0 males at 50 ppm and in both sexes at 75 ppm, attaining statistical significance for body weight gain in males only. Maternal weight gains during gestation were significantly reduced in the 75 ppm group in both generations. A decrease in male mating index was seen in F_1 males at 75 ppm. Decreases in male fertility index, female pregnancy rate and gestation index were observed in both generations at 75 ppm. A greater number of F_1 males in the 50 and 75 ppm groups did not mate in the 10 day cohabitation period. Smaller litter sizes at birth were observed in the 75 ppm groups of both generations with statistical significance attained for F_1 litters (from F_0 dams). Other litter parameters were comparable in all groups. There were no dose-related microscopic changes in females. In males, multifocal degeneration of the seminiferous tubules in the testes was observed in F_1 animals at 75 ppm, which also had increased cell debris in the epididymes. Complete testicular unilateral or bilateral germinal epithelial degeneration/atrophy with only Sertoli cells remaining was seen in 3/30 F_0 and 1/30 F_1 males at 75 ppm and in 1/29 F_0 rats at 50 ppm (none in F_1 MD group). The NOEL for general toxicity and reproduction was 25 ppm (2.1 mg/kg/day) in the diet based on reduced food consumption and decreased mating index at 50 ppm.

Hydramethylnon technical administered as a single oral dose of 0 or 800 mg/kg bw to male rats (10/group) had no significant effect on their reproductive performance when tested 3 weeks after dosing by mating with untreated females, and had no secondary effects on the reproductive performance of untreated female rats bred to these rats.

Two separate 8-week feeding and recovery studies were performed in mature and maturing rats to determine whether pathologic changes of the testes seen in previous studies were due to reduced food intake or to hydramethylnon, and to determine whether these changes were reversible when hydramethylnon was removed from the diet. Hydramethylnon was administered to rats (12/group) in the diet at 0, 200 or 400 ppm for four weeks, with animals retained for a recovery period dosed on untreated diet for an additional four weeks. Additional pair-feeding negative control groups (matching food intake with 200 and 400 ppm groups) were also used in this study. Comparison of results

indicated that maturing rats were more sensitive to testicular atrophy induced by hydramethylnon than mature rats. Testicular atrophy was directly related to hydramethylnon administration and not mediated via reduced weight gain as demonstrated in comparison with pair-fed negative control groups. The testicular pathology was not reversible and appeared to increase in severity with time after dosing ceased, indicating a time lag between dosing and reproductive toxicity. Hepatic cell degeneration caused by hydramethylnon observed in this study at the 400 ppm dose level was reversible.

A teratology study in rabbits was performed, with animals administered 0, 5, 10 or 20 mg/kg bw/d hydramethylnon on days 6 to 18 of gestation by oral gavage. Two dams from the high dose group died in the post-treatment period. Six dams aborted on days 25 to 29 (three in 10 and 20 mg/kg bw/d respectively). Dose-related decrease in mean maternal body weight was noted at 10 and 20 mg/kg bw/d groups, and a reduction in mean maternal body weight gain at 5 mg/kg bw/d. No treatment-related foetal effects were observed. Overall, no NOEL was established for maternotoxicity. A foetal NOEL of 20 mg/kg bw/d (highest dose tested) was established, as hydramethylnon was not teratogenic or foetotoxic at doses ≤20 mg/kg bw/d.

A teratology study in rats was conducted, with animals administered hydramethylnon at 0, 3, 10 or 30 mg/kg bw/d by gastric intubation on gestation days 6-15. Pregnancy rates were similar in all groups. Two females in the high dose group died on gestation days 7 and 16. Mean body weight gains of dams were reduced in the middle and high dose group during the post-dosing interval. Additional maternotoxicity in the high dose group only included red nasal mucous, alopaecia, soft stool and anogenital staining. A small thymus was observed in some high-dose females. An increase in the incidence of rudimentary structures and incompletely ossified supraoccipital bones was noticed in high dose group. The NOEL for maternotoxicity was 10 mg/kg bw/d based on the death and additional maternotoxicity. The compound was not teratogenic or foetotoxic in rats at ≤30 mg/kg bw/d in this study, and a foetal NOEL was established at 30 mg/kg bw/d.

Observation in humans

No information was provided.

Public exposure

Refer to OCS human health risk assessment report.

International regulations

No information was provided.

Scheduling status

Hydramethylnon is currently listed in Schedules 5 and 6.

Hydramethylnon is listed in Schedule 6 of the Poisons Standard except when included in Schedule 5. The Schedule 5 entry for hydramethylnon is for solid baits containing 2 per cent or less of hydramethylnon in welded plastic labyrinths.

Pyriproxyfen is currently listed in Appendix B.

Scheduling history

The following is a record in chronological order of considerations by various committees relating to hydramethylnon.

At the July 1987 meeting of the Drugs and Poisons Scheduling Committee (DPSC), hydramethylnon was considered and placed into Schedule 6 based on irreversible testicular effects observed in several animal species and study duration. A product containing 1.65 % hydramethylnon and enclosed in a welded plastic labyrinth was also considered at this meeting and was determined by the committee as suitable for inclusion in Schedule 5.

The DPSC meeting of February 1988 considered information from the applicant regarding the testicular atrophy seen in immature rats. The company's reply to the committee noted testicular effects in various short-term studies and a reproduction study: however, not all of these studies had been supplied by the sponsor for evaluation. The aforementioned studies were subsequently supplied by the sponsor and evaluated by the NHMRC Toxicology Unit before discussion of hydramethylnon at the May 1989 meeting of the DPSC. It was noted at that meeting that the studies "showed that rats had been immature in the beginning of the study and that the testicular effects were seen in the worst case situation. A simple or brief exposure of immature rats to hydramethylnon at high doses briefly but reversibly impaired fertility in male rats."

In August 1990, the DPSC considered a review of toxicological data in support of two new formulations. Both formulations were available in a welded plastic labyrinth. The committee supported clearance for both of these products.

At the NDPSC meeting in November 1996, the committee considered a request (unsupported by new data) for reconsideration of the Schedule 6 entry for hydramethylnon, in order to accommodate the low acute toxicity profile of a granular ant bait product containing 7.3 g/kg hydramethylnon.

The committee considered previous scheduling discussions for the compound and the toxicity profile for hydramethylnon. The following extract (in Italics) is from the 1996 NDPSC minutes:

> *In previous considerations the Committee considered that with the granular formulation these serious testicular effects occurred at levels which could pose a danger to a small male child in a domestic setting. However, it was noted that repeated exposure was required in the animal studies to cause the sustained testicular effect and a question was raised whether a child was likely to be similarly exposed. In relation to this question it was observed that this end-point would not normally be looked for in a standard acute study but which quite clearly was evident in the shortest of the repeat-dose studies. Hence the critical information lacking was at what point is the onset of the effect and whether or not it can be produced by a single or several acute exposures. Limited information available at the May 1989 NDPSC meeting indicated that a single or brief exposure of rats to hydramethylnon at high doses briefly but reversibly impaired the fertility of male rats.*
>
> *In view of this lack of specific information on testicular atrophy from single high doses which children may access and allowing for species difference, the Committee considered that Schedule 6 remained appropriate.*
>
> *It was the Committee's view that the Schedule 6 classification would not preclude the registration of this product for domestic use under the terms of the NHMRC criteria guidelines for registering such products, because of the need for the specific "POISON" label warning to the consumer.*

Pyriproxyfen, the other active ingredient of the granular ant bait under consideration in this proposal has low toxicity, and was included in Appendix B at the August 1994 NDPSC meeting. The following is a summary of considerations by the committee relating to pyripoxyfen.

The Committee considered toxicological data relating to a submission requesting an exemption from scheduling for pyriproxyfen, a synthetic juvenile hormone analogue which is an insect growth regulator with insecticidal activity against houseflies, fleas, cockroaches and mosquitoes. Pyriproxyfen was intended to be used with an appropriate pesticide (e.g. deltamethrin) to control fleas and cockroaches in domestic, industrial and public health situations.

The Committee noted that pyriproxyfen has low toxicity, is not a skin sensitiser.

The Committee considered that the overall acute toxicity of pyriproxyfen was low, and apart from some liver toxicity at high doses, there was little toxicological concern in repeat-dose studies. The compound was not carcinogenic, mutagenic or teratogenic.

Based on the above toxicity profile, an exemption from scheduling was considered appropriate.

Pre-meeting public submissions

No public submission was received.

Summary of ACCS advice to the delegate

The committee recommended the current scheduling remains appropriate.

Delegate's interim decision

The current Scheduling for hydramethylnon remains appropriate.

An implementation date is unnecessary since no schedule change is proposed.

The reasons for the interim decision comprised the following:

> Hydramethylnon is an insecticide used primarily in ant baits. It is included in both Schedule 5 and 6, the Schedule 6 listing based primarily on concerns of possible testicular toxicity in children. The current submission seeks an amendment to the current Schedule 5 entry, which currently allows for an ant-bait enclosed in a plastic labrynth. The requested amendment to the Schedule 5 entry would allow a granular product (combined with pyriproxyfen) to be used as both a professionally applied product (in Schedule 6) and the same material in a 'shaker pack' for domestic use in Schedule 5.
>
> The delegate notes the advice of the ACCS and agrees that there is a need for the granular product to be retained in Schedule 6 for both domestic and professional use. The ACCS noted that only the professional product currently warns against use in areas where children may be present. Retaining the proposed domestic product in Schedule 6 would ensure that a POISON label warning would be more effective than WARNING in order to alert user to the need for care in using the product, particularly around children.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[7];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

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

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

2.6 Momfluorothrin

Scheduling proposal

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

- In May 2015, 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, requested that the delegate consider creating a new entry for momfluorothrin in Schedule 6 of the Poisons Standard.

Scheduling application

The reasons for the request were:

- An applicant has sought approval for a new active constituent momfluorothrin, a member of the pyrethroid class of chemical. As a new chemical for AgVet use, it will require consideration by the Delegate/ACCS for SUSMP listing prior to final registration of products containing this active constituent.
- While there are no currently proposed products attached to this application, in supporting documents the applicant has foreshadowed that momfluorothrin will be used in household and pest control insecticide products.

Delegate's reasons for referring this to the committee

While the toxicity profile of momfluorothrin is reasonably straightforward, the OCS evaluation report recommends listing in Schedule 6, while the applicant has requested listing in Schedule 5 (with no supporting evidence or argument). The SPF suggests that the delegate refer the submission to the ACCS for advice on resolution of this apparent conflict.

The delegate asked the committee the following questions:

- The scheduling of the synthetic pyrethroids for agricultural use is spread across Schedules 5 to 7, depending primarily on their acute toxicity, and the extent to which product formulation and dilution of their active ingredient reduces the acute poisoning potential. According to the OCS evaluation and SPF guidelines, the acute toxicity of momfluorothrin is consistent with listing in Schedule 6, based on the sex difference in LD_{50} (>30 - <2000 mg.kg female rats; >2000 mg/kg male rats).
- The insecticidal Mode of Action (MoA) for all pyrethroids is neurotoxic, but the OCS evaluation report notes that neurotoxic symptoms in rodents appear to be devoid of any histopathological changes in nerves. The liver tumours observed in rats appear to be associated with a MoA (constitutive androstane receptor activation) that is similar to phenobarbital and the related compound metofluthrin, and would not be relevant to humans at low exposures. Therefore, neither of these would appear to be an issue that drives scheduling.
- If the ACCS agrees that the LD50 in female rats is the critical factor driving scheduling, then listing in Schedule 6 with no cut-off (no product at this stage) is an appropriate recommendation.

Substance summary

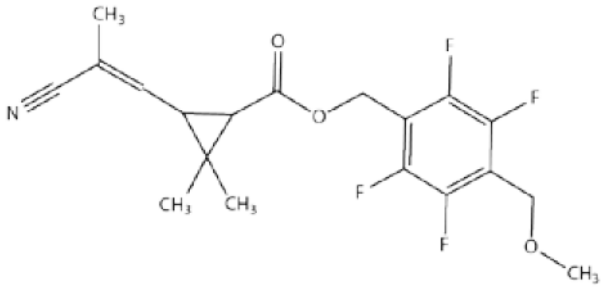

Figure 1: Chemical structure of momfluorothrin

Acute toxicity

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

Toxicity	Species	Momfluorothrin	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	300 < LD_{50} < 2000 mg/kg bw for females LD_{50} > 2000 mg/kg bw for males	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} >2000 mg/kg bw	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	LC_{50} >2030 mg/m3, 4-hour exposure, one death	N/A
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (Maximisation test)	Guinea Pig	Not sensitising	N/A

Repeat-dose toxicity

The systemic toxicity of momfluorothrin in dietary studies consisted primarily of decreased body weight and body weight gain, liver toxicity such as increased liver weight and centrilobular hepatocellular hypertrophy with associated clinical chemistry changes, and thyroid effects (e.g. follicular cell hypertrophy) generally seen at higher dose levels. This systemic toxicity profile was observed in short-term, subchronic and chronic toxicity studies in rats, mice and dogs, with the available data indicating that the rat was the most sensitive species. A short-term inhalational toxicity study identified treatment-related clinical signs suggestive of mild neurotoxic effects (transient tremor, ataxic gait, muscle rigidity and hypersensitivity). No treatment related adverse effects were seen in a short-term dermal toxicity study in the rat at the limit dose.

Mutagenicity

Momfluorothrin was not genotoxic in a bacterial reverse mutation test, and results from the *in vitro* gene mutation assay (in Chinese Hamster V79 cells) and micronucleus test (mice bone marrow cells) were negative. Marginal chromosomal aberration in CHL/IU cells was observed in the *in vitro* chromosomal aberration test performed, though the *in vivo* Unscheduled DNA Synthesis (UDS) assay was negative. Overall, momfluorothrin is not considered genotoxic.

Carcinogenicity

Liver tumours were observed in the 104-week oncogenicity study in rats approaching or exceeding the maximum tolerated dose. There was an increased incidence of hepatocellular adenoma and carcinoma in male rats at 73 and 154 mg/kg bw/day, and in hepatocellular adenomas and carcinomas in female rats at 182 mg/kg bw/day respectively. These tumours were associated with increased liver weight, hepatocellular hypertrophy and an increased incidence of eosinophilic foci in the liver. Momfluorothrin was not carcinogenic in mice and was not mutagenic and/or genotoxic *in vitro* and *in vivo*.

In a series of investigations on the MOA for the liver tumours in rats, it has been proposed that treatment with momfluorothrin induced cytochrome P450 (CYP) CYP2B isoform, which was shown to involve activation of the constitutive androstane receptor (CAR) in rat hepatocytes. This resulted in increased liver weights which were associated with centrilobular hepatocyte hypertrophy and induction of increased hepatocellular DNA replication leading to tumour formation. This MOA is similar to that of phenobarbital, which is known to be non-genotoxic, a CAR activator and an inducer of liver CYP2B isoforms. The OCS has evaluated the proposed MOA, and notes the data in support of the postulated MOA and the similarities to the MOA identified for the related compounds metofluthrin and phenobarbital. Overall, the OCS considers that the available data supports the proposal that momfluorothrin-induced rat liver tumours occur via a MOA that is similar to phenobarbital and that it is plausible that the MOA is not relevant to humans. Thus, momfluorothrin is not expected to increase hepatocellular proliferation and, thus, pose a carcinogenic risk to humans.

Reproduction and developmental toxicity

Momfluorothrin was not a reproductive or developmental toxicant. However, in the developmental toxicity study in the rat, clinical signs including tremors were noted (suggestive of a neurotoxic effect) in maternal animals, though development was not affected at maternotoxic doses.

Neurotoxicity

While no neurotoxic effects were observed in the sub-chronic 13 week dietary study in rats, the acute oral (gavage) neurotoxicity study identified several neuro-functional changes, including tremors, salivation and straub tail at the highest dose level of 200 mg/kg bw tested in the acute neurotoxicity study, though no treatment-related neuro-histopathological changes were observed. Overall, when considered with the tremors noted in the rat developmental toxicity study and other acute/short term toxicity studies in the rat, the data available suggests that momfluorothrin has mild neurotoxic potential. In this context, it is possible that momfluorothrin has similar neurotoxic effects to other pyrethroids.

Observation in humans

No information provided.

Public exposure

No information was provided.

International regulations

Momfluorothrin has recently been registered by the US EPA (Attachment B) and Health Canada.

Scheduling status

Momfluorothrin is not scheduled.

Scheduling history

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

Pre-meeting public submissions

No public submission was received.

Summary of ACCS advice to the delegate

The committee recommended a new S6 entry be created for momfluorothrin.

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Meets criteria for Schedule 6 due to acute oral toxicity.

Delegate's interim decision

Schedule 6—New Entry

MOMFLUOROTHRIN

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

The proposed implementation date is 1 February 2016. An early implementation date is proposed to facilitate registration of momfluothrin as an active ingredient by the APVMA.

The reasons for the interim decision comprised the following:

> The toxicological profile of momfluothrin is well characterised in the OCS evaluation report. Much of the toxicity profile is consistent with SPF criteria for listing in Schedule 5. However, the LD50 in female rats is in the Schedule 6 range and the delegate agrees with the ACCS recommendation, that monfluothrin should be listed in Schedule 6 at this time. It may be possible to consider a lower schedule for products with a low percentage content of momfluothrin at a later time.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

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

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

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

2.7 Carcinogenic amines (azo dyes)

Scheduling proposal

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

- In April 2015 the delegate received a request to consider new entries for various dyes that could release selected carcinogenic amines and/or aromatic amine precursors for listing in Schedule 7 or Schedule 10/Appendix C.

Scheduling application

The reasons for the request were:

- that whilst the data for the actual dyes are limited, the chemicals are all considered to have the potential to be metabolised to the following carcinogenic and/or genotoxic aromatic amines through reductive cleavage of the azo linkage;
  - *o*-anisidine (CAS No. 90-04-0);
  - *o*-toluidine (CAS No. 95-53-4);
  - *p*-aminoazobenzene (CAS No. 60-09-3);
  - *o*-aminoazotoluene (CAS No. 97-56-3);
  - 2,4-toluenediamine (CAS No. 95-80-7);
  - 5-nitro-*o*-toluidine (CAS No. 99-55-8);
  - *p*-chloroaniline (CAS No. 106-47-8); and
  - 4-chloro-*o*-toluidine (CAS No. 95-69-2).
- the scheduling of these dyes would be consistent with scheduling decisions on other azo dyes that have the potential to be metabolised to known carcinogens;
- that restrictions on using some of these chemicals exist overseas, with some restrictions based on the absence of adequate data to demonstrate safety; and
- that trace levels of the aromatic amines used in the production of the dyes could be technologically inevitable.

Delegate's reasons for referring this to the committee

This is a complex scheduling matter that proposes listing in Schedule 7. The SPF recommends that such matters be referred to an advisory committee. Furthermore, the way the chemicals are listed for scheduling and the potential regulatory impacts are both matters on which the delegate requests ACCS advice.

The delegate asked the committee the following questions:

- The NICNAS proposals for listing all the specified aromatic amines in Schedule 7 and/or Schedule 10, is to capture their use in dyes that may be metabolised to the listed aromatic amines. All are alleged to have genotoxic and/or carcinogenic properties that warrant restrictive scheduling. Does the ACCS agree that the genotoxic/carcinogenic potential of **all** the dyes supports such actions, and if not, which ones should be included in either Schedule 7 or 10?
- Note that one of the specified amines (4-chloro-o-toluidine) is already listed in Schedule 7, but there is no indication in scheduling records of when, or why, this listing was made. Depending on how the ACCS proposes actions on the other listed amines, is there a need to amend the current S7 listing of 4-chloro-o-toluidine for consistency?
- If they are to be included in Schedules 7/10, is the most appropriate way to list them individually, as in the public notice, or to create an entry analogous to that recommended at the November 2013 and 2014 ACCS meetings, where specific azo dyes that could be metabolised to benzidine or benzidine-congeners were listed in Schedule 7 under generic entries.
- Note that the ACCS recommendation on dyes that could be metabolised to benzidine was based on knowledge that benzidine is a known human carcinogen. Is the strength of evidence for carcinogenicity for the listed aromatic amines in this current scheduling proposal of the same compelling nature?
- To what extent could the REACH approach to classification in Annex XVII inform the way that these dyes could be listed in the SUSMP schedules?

Unless specifically included in the schedule wording, listing in Schedules 7 or 10 implies that the entries would capture products that contain the chemicals as an impurity or residual reaction product. What regulatory impact would such listing impose on products with residual contaminants if the ACCS recommends listing of the individual aromatic amines? Is there any basis for recommending scheduling cut-offs below which the restrictive scheduling would not apply?

Substance summary

Refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) human health Tier II assessment reports for:

- Dyes that could release selected carcinogenic amines (listed on AICS) NICNAS IMAP assessment ID 1418;
- *o*-anisidine (CAS No. 90-04-0) NICNAS IMAP assessment ID 1161;
- *o*-toluidine (CAS No. 95-53-4) NICNAS IMAP assessment ID 1158;
- *p*-aminoazobenzene (CAS No. 60-09-3) NICNAS IMAP assessment ID 1165;
- *o*-aminoazotoluene (CAS No. 97-56-3) NICNAS IMAP assessment ID 1166;
- 2,4-toluenediamine (CAS No. 95-80-7) NICNAS IMAP assessment ID 831;
- 5-nitro-*o*-toluidine (CAS No. 99-55-8) NICNAS IMAP assessment ID 1354;
- *p*-chloroaniline (CAS No. 106-47-8) NICNAS IMAP assessment 1157; and
- 4-chloro-*o*-toluidine (CAS No. 95-69-2) NICNAS IMAP assessment ID 1098.

The critical concern for this group of chemicals relates to potential carcinogenic effects following exposure. Toxicological data are available for several of the chemicals: Solvent Red 24; Solvent Red 23; Solvent Red 1; Solvent Red 19; Orange Oil SS; Basic Red 76; Acid Red 73; Acid Red 35; Disperse Yellow 7; CAS No. 56358-09-9; and CAS No. 70879-65-1, which are considered representative of the potential for toxicity due to azo cleavage for all chemicals in this group. The data from the structurally-related

chemicals and aromatic amines (azo cleavage products), the *p*-aminoazobenzene; *o*-anisidine; *o*-toluidine; 4-toluenediamine; *o*-aminoazotoluene; 5-nitro-*o*-toluidine; 4-chloro-*o*-toluidine; and *p*-chloroaniline are also included.

Genotoxicity

Based on the limited data available, it is not possible to draw a definite conclusion regarding the genotoxicity of the chemicals in this group. Although available data are neither sufficient nor adequately comprehensive for classification, a genotoxic mode of action cannot be ruled out.

Carcinogenicity

The chemicals identified by CAS No. 85136-74-9; CAS No. 108225-03-2; and CAS No. 118658-99-4 are classified as hazardous—Category 2 carcinogenic substances—with the risk phrase 'May cause cancer' (T; R45) in the HSIS (Safe Work Australia). No experimental data are available to evaluate or to support an amendment to this classification.

Limited data are available on the chemicals in this group. The carcinogenic potential of Solvent Red 23 (*p*-aminoazobenzene-based); Solvent Red 19 (*p*-aminoazobenzene-based); Disperse Yellow 7 (CAS No. 6300-37-4) (*p*-aminoazobenzene-based); Solvent Red 24 (*o*-anisidine-based); and Orange Oil SS (*o*-toluidine-based) have been examined in long-term oral and dermal studies in mice and rats.

The strongest evidence for carcinogenicity was reported for Orange Oil SS. The chemical was found to be carcinogenic in mice, with intestinal and local tumours identified following oral and subcutaneous administration, respectively. The chemical also produced tumours in the mouse urinary bladders following bladder implantation. Studies in rats were inadequate for evaluation. Whilst both positive and negative results have been observed for other chemicals in this group, studies generally were considered inadequate for evaluation (IARC, 1975; Government of Canada, 2011; Government of Canada, 2013a).

The aromatic amine *o*-toluidine that could be formed following azo bond reductive cleavage in some of the chemicals in this group, is recommended for classification as a category 1 carcinogenic substance based on the evidence for carcinogenicity in humans.

Seven of these aromatic amines (*p*-aminoazobenzene; *o*-anisidine; *o*-toluidine; 2-4-toluenediamine; *o*-aminoazotoluene; 4-chloro-*o*-toluidine; and *p*-chloroaniline) are classified as hazardous (Category 2 carcinogenic substance) with the risk phrase 'May cause cancer' (T; R45) in the HSIS (Safework Australia). The chemical 5-Nitro-*o*-toluidine is classified as hazardous (Category 3 carcinogenic substance) with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40) (Safe work Australia).

The available experimental data (animal studies) for these aromatic amines identifies a number of chemically-induced multi-organ tumours. These include benign and malignant tumours in the urinary bladder, spleen, subcutaneous tissues, kidneys, adrenal gland, liver, mammary glands, skin, blood and blood vessels, thyroid, lungs, gallbladder and renal pelvis.

Findings from several cohort studies involving factory workers have provided strong evidence for an increased risk of urinary bladder cancer associated with long-term occupational exposure to o-toluidine.

The mechanism of action underlying the carcinogenicity of these aromatic amines is still not fully understood. However, metabolic activation to produce nitrenium ion metabolites, which cause DNA adduct formation and induction of DNA damaging effects, has been suggested. A genotoxic mode of action cannot be dismissed.

Overall, based on the potential for the chemicals to be metabolised to form classified carcinogens, classification is considered appropriate.

Public exposure - Cosmetic and domestic

Some of the chemicals in this group (Solvent Red 23; Solvent Red 24; CAS No. 131-79-3; Solvent Red 1; Orange Oil SS; CAS No. 4482-25-1; CAS No. Acid Red 73; CAS No. Acid Red 35; CAS No. 8005-78-5; and Basic Red 76) have been identified as having potential cosmetic use. In Australia, Acid Red 35 and Basic Red 76 have reported use in hair dyes. A recent international use of Solvent Red 23 and Orange Oil SS in hair dyes was also reported.

Some of the potential cleavage products or impurities of the chemicals in this group (aromatic amines) such as *o*-toluidine; *p*-aminoazobenzene; *o*-aminoazotoluene; and *p*-chloroaniline have been detected in a number of cosmetic products. The chemical *o*-toluidine was detected in permanent hair dyes and commercial henna samples (colours not specified). Hence, the public could potentially be exposed to classified carcinogens as an impurity in, or through the release of, these aromatic amines derived from the chemicals in this group. In addition, *o*-aminoazotoluene in decorative colouring (alta) used by Asian women on their feet has been reported. 'Certain imported products with cultural significance in some communities may result in increased risk for these populations'.

Based on the available data, widespread domestic use is not expected; however, the introduction of these dyes for home use cannot be excluded.

International regulations

Cosmetic

Based on the information obtained from Galleria Chemica, the chemicals Solvent Red 24 (CAS Nos. 85-83-6) and Solvent Red 23 are listed in the Health Canada List of prohibited and restricted cosmetic ingredients (the cosmetic ingredient "Hotlist").

The chemicals Solvent Red 24; Solvent Red 23; Solvent Red 1; CAS No. 4482-25-1; CAS No. 5413-75-2; CAS No. 5421-66-9; CAS No. 8005-78-5; CAS No. 85136-74-9; CAS No. 68425-18-3; CAS No. 118658-98-3; CAS No. 118658-99-4 are listed in the:

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

The chemicals Solvent Red 24; CAS No. 85136-74-9; CAS No. 108225-03-2; and CAS No. 118658-99-4 are prohibited for all uses, whereas the other chemicals are prohibited when used as a substance in hair dye products.

The chemical Solvent Red 23 (identified as CI 26100) is listed in the:

- ASEAN Cosmetic Directive Annex IV Part 1—List of colouring agents allowed for use in cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of colourants allowed in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 6—Colouring agents cosmetic products may contain with restriction.

In the above directives, the chemical is specified as 'not to be used in products applied to mucus membranes'; purity criteria also apply.

The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP 2002) concluded that 'azo dyes which may release one or more carcinogenic aromatic amines, poses a risk to the health

of the consumer'. In 2004, the SCCNFP concluded that several of the dyes cannot be considered safe for hair dyeing purposes, unless they are regarded as such on the basis of an adequate safety dossier. These include:

- Solvent Red 1 (o-anisidine-based);
- Solvent 23 and Acid Red 73 (p-aminoazobenzene-based); and
- CAS No. 8005-78-5 and CAS No. 4482-25-1 (2,4-toluenediamine-based).

Basic Red 76 is listed in the EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down. The chemical is allowed in non-oxidative hair dye products at a maximum concentration of 2 %.

In 2011, the European Scientific Committee on Consumer Safety (SCCS) concluded that 'Basic Red 76 containing up to 18% methyl sulphate does not pose a risk to the health of the consumer when used as a non-oxidative hair dye with a maximum on-head concentration of 2.0%.' (SCCS, 2011). However, this opinion did not directly consider the release of o-anisidine from reductive cleavage of the azo linkage. Whilst quantitative risk calculations conducted by the Government of Canada estimated a margin of exposure of 10000 for cancer effects for the use of Solvent Red 1 in hair conditioner (concentration 0.1%) (Government of Canada, 2013a), in the absence of Australian specific use data, it is not possible to extrapolate this finding for Australia.

The chemicals Solvent Red 24; Solvent Red 23; and CAS No. 131-79-3 are listed in the Philippines Restricted Ingredients For Use In Cosmetics—List of substances which must not form part of the composition of cosmetic products.

Other

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

> '*1. Azodyes which, by reductive cleavage of one or more azo groups, may release one or more of the aromatic amines listed in Appendix 8, in detectable concentrations,*
>
> *i.e. above 30 ppm in the finished articles or in the dyed parts thereof, according to the testing methods listed in Appendix 10, shall not be used in textile and leather articles which may come into direct and prolonged contact with the human skin or oral cavity, such as:*
>
> - *clothing, bedding, towels, hairpieces, wigs, hats, nappies and other sanitary items, sleeping bags;*
> - *footwear, gloves, wristwatch straps, handbags, purses/wallets, briefcases, chair covers, purses worn round the neck;*
> - *textile or leather toys and toys which include textile or leather garments; and*
> - *yarn and* fabrics intended for use by the final consumer.
>
> *2. Furthermore, the textile and leather articles referred to in paragraph 1 above shall not be placed on the market unless they conform to the requirements set out in that paragraph.*'

The chemicals *o*-anisidine; *o*-toluidine; *p*-aminoazobenzene; 2,4-toluenediamine; *o*-aminoazotoluene; 5-nitro-*o*-toluidine; *p*-chloroaniline; and 4-chloro-*o*-toluidine are listed in Appendix 8 of EU REACH Annex XVII.

The chemicals identified by CAS No. 85136-74-9; CAS No. 108225-03-2; and CAS No. 118658-99-4 are restricted under Annex XVII to the REACH Regulations. '*The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations 0.1 %*' (European Parliament and Council 1999; European Parliament and Council 2006; European Parliament and Council 2008).

Scheduling status

The chemicals proposed for scheduling consideration are not currently specifically scheduled. However, other azo dyes that have the potential to be metabolised to known carcinogens have previously been considered for scheduling and listed in Schedule 7. These other azo dyes include:

BENZIDINE-BASED AZO DYES being:

- 2,2'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[N-(4-chlorophenyl)-3-oxobutanamide]
  - CAS No. 94249-03-3
- Acid Red 85 (Acid Fast Red A)
  - 1,3-Naphthalenedisulfonic acid, 7-hydroxy-8-[[4'-[[4-[[(4-methylphenyl)sulfonyl]oxy]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-, disodium salt
  - CAS No. 3567-65-5
- Direct Black 38
  - 2,7-Naphthalenedisulfonic acid, 4-amino-3-[[4'-[(2,4-diaminophenyl)azo][1,1'-biphenyl]-4-yl]azo]-5-hydroxy-6-(phenylazo)-, disodium salt
  - CAS No. 1937-37-7
- Direct Blue 2
  - 2,7-Naphthalenedisulfonic acid, 5-amino-3-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-4-hydroxy-, trisodium salt
  - CAS No. 2429-73-4
- Direct Blue 6
  - 2,7-Naphthalenedisulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[5-amino-4-hydroxy-, tetrasodium salt
  - CAS No. 2602-46-2
- Direct Brown 2
  - 5-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxy-benzoic acid disodium salt
  - CAS No. 2429-82-5
- Direct Brown 95
  - Cuprate(2-), [5-[[4'-[[2,6-dihydroxy-3-[(2-hydroxy-5-sulfophenyl)azo]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxybenzoato(4-)]-, disodium salt
  - CAS No. 16071-86-6
- Direct Green 1
  - 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-3-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-6-(phenylazo)-, disodium salt
  - CAS No. 3626-28-6
- Direct Green 6

- 2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-6-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-3-[(4-nitrophenyl)azo]-, disodium salt
- CAS No. 4335-09-5

· Direct Red 28 (Congo Red)

- 1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[4-amino-, disodium salt
- CAS No. 573-58-0

· Direct Red 37

- 1,3-Naphthalenedisulfonic acid, 8-[[4'-[(4-ethoxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-7-hydroxy-, disodium salt
- CAS No. 3530-19-6

Scheduling history

In April 2014, the delegate, based on ACCS advice, made a decision to list 11 benzidine-based dyes in Schedule 7. The delegate indicated that inclusion of benzidine-based dyes in Schedule 10/Appendix C was not the most appropriate way of regulating the use of these substances. The delegate also noted that some of the dyes may have use as laboratory and analytical reagents. While there are stringent existing controls under Model Work Health and Safety legislation, and industry advises that they have been largely phased out of many uses, their carcinogenic potential, via conversion to benzidine (a known human carcinogen), indicates they should not be used in products available in the domestic market.

The delegate confirmed a proposed implementation date of 1 June 2015 for the following benzidine-based dyes:

Schedule 7—New entry

BENZIDINE-CONGENER (3,3'-disubstituted) AZO DYES.

Schedule 7—Amend Entry

BENZIDINE-BASED AZO DYES being:

C. I. ACID BLACK 29. CAS No. 12217-14-0

Note that the amendment to the current Schedule 7 BENZIDINE-BASED AZO DYES entry is to add the chemical C.I. Acid Black 29 to the existing list.

Public pre-meeting submissions

One public submission was received. The submission stated concern for the sheer number of compounds being considered for scheduling and that there is a lack of resources for a thorough consideration of each. Scheduling is posed to be delayed to enable more time for this. Two dyes were singled-out in the submission, CAS# 85-85-9 and CAS# 68391-30-0, where each are allowed, in some degree, in the EU. These dyes, and any others that may also be permitted in any degree, be exempt from Appendix C listing.

The public submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended a new Schedule 7 be created for azodyes that are derivatives by diazotisation from the substances listed in the resolution.

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Potential widespread ability to substitute.
- Carcinogenic potential.

Delegate's interim decision

The NICNAS IMAP program has referred for possible listing in Schedule 7, a number of azo dyes that can be reduced by azo reductases to carcinogenic components. The delegate has previously considered, and agreed to, Schedule 7 listing a number of benzidine-and benzidine-congener azo dyes. The current proposal seeks to regulate azo dyes that can be reduced by azo reductases to 8 specific carcinogenic aromatic amines: o-anisidine (CAS No. 90-04-0); o-toluidine (CAS No. 95-53-4); p-aminoazobenzene (CAS No. 60-09-3); o-aminoazotoluene (CAS No. 97-56-3); 2,4-toluenediamine (CAS No. 95-80-7); 5-nitro-o-toluidine (CAS No. 99-55-8);p-chloroaniline (CAS No. 106-47-8);and 4-chloro-o-toluidine (CAS No. 95-69-2). One of these (4-chloro-o-toluidine) is already listed in Schedule 7 under the name used in connection with its use as a pesticide (chlordimeform). The others are not currently scheduled, presumably because they are only used in industrial processes, and not in products available to the public. Some of these substances are listed in Appendix 8 of EU REACH Annex XVII, suggesting that actions will be taken by industry to phase out many of their uses.

The delegate accepts ACCS advice that the dyes referred in the current submission should also be controlled for use in consumer products by listing in Schedule 7, and agrees that a generic listing (like the current Schedule 7 entries for benzidine-congener azo dyes) could achieve this objective. Simply listing the 7 specified aromatic amines in Schedule 7 as separate entries would not necessarily capture the parent azo dyes as 'derivatives'.

Schedule 7—New Entry

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

- o-anisidine (CAS No. 90-04-0)
- o-toluidine (CAS No. 95-53-4)
- p-aminoazobenzene (CAS No. 60-09-3)
- o-aminoazotoluene (CAS No. 97-56-3)
- 2,4-toluenediamine (CAS No. 95-80-7)
- 5-nitro-o-toluidine (CAS No. 99-55-8)
- p-chloroaniline (CAS No. 106-47-8)
- 4-chloro-o-toluidine (CAS No. 95-69-2).

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

Proposed implementation date is 1 February 2016. This implementation date is warranted since the objective is to remove any such products from the Australian market on safety grounds.

The reasons for the interim decision comprised the following:

> This wording specifically captures azo dyes that can be reduced by azo reductases to aromatic amines that could pose a cancer risk to the general public through their use in consumer products (e.g textiles, leathers, fabrics). At this time, there appears to be no need to list the individual

aromatic amines in Schedule 7 in the absence of any information that they are used in consumer products in their own right.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

One submission was received. The submission did not support the delegate's interim decision. The submission states the implementation date is problematic for industry as it does not allow sufficient time for manufacturers to identify products that will be affected by the scheduling decision and allow a time to implement a substitute colourant. The submission was also concerned with two listed azo dyes in particular, CAS numbers 85-85-9 and 68391-30-0, that are permitted in for use in Europe and that there is insufficient evidence to include these in Schedule 7. Furthermore, the submission is concern that the scheduling entry is broadly worded—referring to 'diazotisation' reaction—and may capture substances that are listed elsewhere in the SUSMP.

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

Delegate's final decision

The delegate notes the submission received in response to publication of the interim decision and confirms the interim decision as the most pragmatic approach to controlling the substances under consideration. The delegate believes that a generic entry, similar to that previously used for the Schedule 7 entry for benzidine-congener azo dyes is preferable to individually listing all the affected dyes. The delegate notes the concerns that substances described in the generic entry may be difficult for industry to identify, but points to the NICNAS IMAP report that lists all 72 dyes on the Australian Inventory of Chemical Substances (AICS) that would be included in the generic entry.

The submission lists two dyes (CAS 85-85-9 and Basic Red 76 CAS 6831-30-0) that are on an EU list of substances allowed in hair dye products, with a maximum concentration proposed. Only Basic Red 76 is on the NICNAS list, and would be affected by the proposed Schedule 7 entry. The delegate suggests that if this dye is of importance to the Australian industry, a submission should be made to exempt this specific substance from the proposed Schedule 7 generic entry, with proposals on how it should be regulated. The submission also states that hair dyes based on 4-amino-m-cresol (CAS 2835-99-6) would be captured by the generic entry. This is not the case, since it is not an azo dye listed in the NICNAS IMAP report, and it is not one of the three o-toluidine amines listed as potential products of azoreduction of the dyes that are subject to the NICNAS report.

The submission also requests a longer implementation period to allow for re-formulation of products containing the affected azo dyes. However, consistent with the previous decisions relating to benzidine- and benzidine congener-based azo dyes, the delegate confirms that an early implementation date is required for the protection of public health from potentially carcinogenic amines that could be released by these azo dyes.

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

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

2.8 Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)

Scheduling proposal

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

- In April 2015 the delegate received a request to consider creating a new entry for quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)- in Schedule 6, with appropriate cut-off exemptions when used in low concentrations.

Scheduling application

The reasons for the request were:

- The chemical is a skin irritant and slight eye irritant, consistent with Schedule 5 factors.
- The chemical is a skin sensitiser, consistent with Schedule 6 factors.

The NICNAS recommended usage concentrations of 0.03% in fine fragrances, 0.006% in other cosmetic products and 0.00075% in household products correspond to the maximum proposed usage concentrations by the notifier. The NICNAS assessment determined that there was no unreasonable risk to the public when used at these concentrations.

A margin of exposure (MoE) value of ≥ 100 was considered acceptable to account for intra- and inter-species differences. Using an NOAEL of 150 mg/kg bw/day, which was derived from a 28-day oral repeat dose toxicity study in rats, and an estimated exposure value of 0.018 mg/kg bw/day from use of the chemical in cosmetic and household products, a MoE of 8,343 was estimated. A quantitative risk assessment for skin sensitisation also indicated that use of the chemical at the proposed concentrations was not considered to be unreasonable.

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

Delegate's reasons for referring this to the committee

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

The delegate asked the committee the following questions:

- Does the ACCS consider that the toxicological profile of quinolone, 5,6,7,8-tetrahydro-8-(1-methylpropyl)- is sufficiently similar to the seven fragrance chemicals where no scheduling action was recommended, or is it more like 4,4-dimethyl-1-cyclohexene-1 propanal, where listing in Schedule 6 was recommended, along with different product-related exemption cut-offs?

- If scheduling is recommended, is the chemical name quinolone, 5,6,7,8-tetrahydro-8-(1-methylpropyl)- the preferred name for listing (or some other name)?
- Does the ACCS support different exempt cut-offs for a Schedule 6 entry for different product types, as proposed in the NICNAS report?

Substance summary

Please refer to the New Chemical assessment report for Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl). This report is publicly available on the NICNAS website: NICNAS New Chemical Report.

Acute toxicity

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

Toxicity	Species	Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	> 2000	None
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Not provided	Not provided	
Skin irritation	Rabbit	Irritating	Consistent with S5
Eye irritation	Rabbit	Slightly irritating	Consistent with S5
Skin sensitisation (Local lymph node assay)	Mouse	Evidence of sensitisation (EC3 = 6.1%)	Consistent with S6

Repeat dose toxicity

A 28-day repeat dose study by oral gavage was conducted in rats with the chemical at dose levels of 15, 50 and 150 mg/kg bw/day. Based on the results of this study, the No Observed Adverse Effect level was established at 150 mg/kg bw/day as the observed changes noted in the mid- and high-dose groups were either completely reversible or showed definitive trends towards reversibility. Furthermore, the changes were considered to be largely stress related rather than changes of systemic toxicity.

Mutagenicity

The chemical was not mutagenic in a bacterial reverse mutation assay.

Genotoxicity

The chemical was not clastogenic in an in vitro mammalian chromosome aberration test.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

There will be widespread and repeated exposure of the public to the chemical (at ≤ 0.03% concentration) through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposures (e.g. through the use of spray products) are also possible.

International regulations

No information was provided.

Scheduling status

Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)- is not specifically scheduled. There is only one fragrance chemical currently listed in the Poisons Standard (see notes below). Where other quinolone derivatives have been listed in the Schedules (usually in Schedules 2, 3, 4 or 10), it relates to therapeutic uses of 8-hydroxyquinolines or quinolone antibiotics.

Scheduling history

Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)- has not been previously considered for scheduling hence a scheduling history is not available.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended the substance does not require scheduling.

Delegate's interim decision

The reasons for the interim decision comprised the following:

> This is one of three fragrance ingredients considered by the ACCS at the August 2015 meeting, and the only one where the recommendation was not to schedule. Only the skin/eye irritancy and sensitising potential are consistent with listing in Schedules 5 and 6, but the very low concentrations likely to be present in cosmetics and consumer products indicate there would be large margins of safety. The delegate has therefore decided to maintain consistency with previous decisions on fragrance ingredients and to accept ACCS advice that this fragrance ingredient does not need to be controlled via scheduling.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

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

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

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

2.9 4-amino-*m*-cresol (Phenol, 4-amino-3-methyl)

Scheduling proposal

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

- In April 2015 the delegate received a request to consider creating a new entry for 4-amino-*m*-cresol in Schedule 5 to include use in hair dyes and eyelash colouring products with an appropriate cut-off.

Scheduling application

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

- A proposal to create a new entry for 4-amino-*m*-cresol in Schedule 5 to include use in hair dyes and eyelash colouring products with an appropriate cut-off.

The reasons for the request were:

- the chemical has reported cosmetic use in permanent hair dye preparations in Australia;
- the chemical is a moderate skin sensitiser;
- only limited data are available on eye and skin irritation; with a 1.5 % concentration the chemical may have a minimal eye irritation potential;
- there is a lack of data on acute or repeated dose dermal and inhalation toxicity; and
- the overseas restrictions for use of this chemical in hair dyes state that the maximum concentration allowed in an oxidative hair dye substance is 1.5 % (after mixing with hydrogen peroxide).

The critical health effect for risk characterisation is skin sensitisation. Given the potential for induction and elicitation of sensitisation even below the overseas restriction cut-off, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical below the cut-off. This is consistent with Schedule 6 entries for some other hair dye ingredients.

Delegate's reasons for referring this to the committee

The toxicological issues in this scheduling proposal are similar to those considered by the ACCS in November 2013 for 2-amino-5-ethyl-phenol and in July 2014 for o-aminophenol and for 5-amino-2-methyl-phenol at this meeting. The delegate's reasons for referring the current proposal for 4-amino-*m*-cresol are similar, in that it is an ingredient in hair dyes and cosmetic products for dyeing eyebrows

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

and eyelashes and it has the following toxicological issues: acute toxicity and sensitisation potential. The NICNAS recommendation was for scheduling controls to restrict use in hair dye and other cosmetic preparations. Its use in cosmetics is restricted in various overseas regulations. ACCS advice is needed to determine the optimal scheduling actions to achieve the requested controls.

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 4-amino-*m*-cresol (acute toxicity, sensitisation potential, negative mutagenicity but limited information on skin-eye irritancy and carcinogenicity) warrants controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of moderate skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- Does the ACCS consider that including 4-amino-*m*-cresol in Schedule 6 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 1.5%, as suggested in the NICNAS report?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Which of the names in the NICNAS IMAP report should be used for any schedule entry? e.g. 4-amino-*m*-cresol, 4-amino-*o*-cresol or 4-hydroxy-*o*-toluidine?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

Refer to the NICNAS IMAP report available on the NICNAS website: NICNAS IMAP assessment ID 1040.

Acute toxicity

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

Toxicity	Species	Phenol, 5-amino-2-methyl	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	870 mg/kg bw	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	Guinea pig	Not irritant at concentrations up to 3 % (limited data)	N/A
Eye irritation	Guinea pig	Minimal irritant potential at 1.5 %	Schedule 5

Skin sensitisation

The chemical is a skin sensitiser based on the data from the NICNAS IMAP report.

A local lymph node assay (LLNA) with the chemical was conducted in CBA/J mice (OECD TG 429). The chemical was mixed either with water/acetone (1:1) and olive oil (4:1) or with DMSO and administered at the final concentrations of 0.5, 1.5, 3 or 5 % and 0.5, 1.5, 5 or 10 %, respectively. The estimated concentration required to produce a stimulation index of three (EC3) was 2.15 % when a mix of water/acetone/olive oil was used as a vehicle, and 1.45 % when DMSO was used as a vehicle. The chemical is, therefore considered to be a moderate skin sensitiser.

Repeat-dose toxicity

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

Genotoxicity

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

Carcinogenicity

Based on the available genotoxicity data and information available from Quantitative Structure Activity Relationship (QSAR) modelling, the chemical is not considered to be carcinogenic.

Reproductive and developmental toxicity

Based on a single prenatal developmental toxicity study available, the chemical is not expected to cause reproductive or developmental toxicity at the doses tested. However, the Scientific Committee on Consumer Products (SCCP) opinion stated that this study did not use the dose selection according to the OECD test guidelines and therefore, 'a possible hazard is not adequately identified'.

Public exposure

The chemical is reported to be used in permanent hair dye preparations in Australia. The chemical may also be in products to colour eyelashes.

New Zealand and the European Union have restricted the use of this chemical in cosmetics. The chemical, once mixed under oxidative conditions, should not exceed 1.5 % in hair dyes or eyelash products (CosIng).

If the chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic compounds could be formed.

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

International regulations

The chemical is listed on the following:

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III Part 2—List of substances provisionally allowed;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: '(a) Hair dye substance in oxidative hair dye products; (b) Products intended for colouring eyelashes; For (a) and (b): After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 1.5%; (b) For professional use only'; and

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

Scheduling status

4-amino-*m*-cresol is not specifically scheduled.

Scheduling history

4-amino-*m*-cresol has not been previously considered for scheduling; therefore, scheduling history is not available.

Public pre-meeting submissions

One public submission was received. The submission stated that there were no objections to aligning Australian scheduling with those of the EU.

The public submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended a new Schedule 6 entry be created for 4-amino-*m*-cresol, except in preparations containing 1.5% or less of the substance after mixing for use when the containers are labelled with the appropriate warning labels.

The committee also recommended appropriate Appendix E and Appendix F statements (provided below) for 4-amino-m-cresol are to be created.

Appendix E, Part 1—New Entry

Poison	Standard Statement
4-AMINO-*M*-CRESOL	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 – If in eyes wash out immediately with water

Appendix F, Part 1—New Entry

Poison	Warning Statement
4-AMINO-*M*-CRESOL	28 - (Over) (Repeated) exposure may cause sensitisation.

The committee also recommended changing the name from its original reference of phenol, 4-amino-3-methyl is 4-AMINO-*M*-CRESOL.

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Hair dye, eyelash and eyebrow tinting products
- Fits the criteria in Schedule 6: skin sensitiser and acute oral toxicity.

Delegate's interim decision

The Committee recommended a new Schedule 6 entry be created for 4-amino-m-cresol with appropriate exempt cut-offs as follows:

Schedule 6—New Entry

4-AMINO-*M*-CRESOL in hair dyes and eyebrow/eyelash colouring preparations **except**:

a) in hair dye preparations containing 1.5% or less of 4-amino-*m*-cresol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

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

b) in eyelash and eyebrow tinting products containing 1.5% or less of 4-amino-m-cresol after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

Written in letters not less than 1.5mm in height.

Appendix E, Part 1—New Entry

Poison	Standard Statement
4-AMINO-*M*-CRESOL	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 – If in eyes wash out immediately with water

Appendix F, Part 1—New Entry

Poison	Warning Statement
4-AMINO-*M*-CRESOL	28 - (Over) (Repeated) exposure may cause sensitisation.

The delegate considered the relevant matters under subsection 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 the substance.

The proposed implementation date is 1 June 2016. A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

The reasons for the interim decision comprised the following:

4-amino-m-cresol is an ingredient of oxidative hair dyes. In common with other amine hair dye ingredients, there is a risk of skin/eye irritation and skin sensitisation. This risk has been managed for other oxidative hair dye ingredients by listing in Schedule 6, with 'reverse scheduling'

provisions that exempt some preparations when labelled with appropriate warning statements. The delegate accepts ACCS advice that 4-amino-m-cresol scheduling should be managed in the same way as previously scheduled hair dye ingredients.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

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

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

Delegate's final decision

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

2.10 4-amino-2-hydroxytoluene (Phenol, 5-amino-2-methyl)

Scheduling proposal

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

- In February 2015 the delegate received a request to consider creating a new entry for 4-amino-2-hydroxytoluene in Schedule 6 to include use in hair dyes and eyelash colouring products.

Scheduling application

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

- A proposal to create a new entry for 4-amino-2-hydroxytoluene in Schedule 6 to include use in hair dyes and eyelash colouring products.

The reasons for the request were:

- the chemical has reported cosmetic use in permanent hair dye preparations in Australia;
- the chemical is a strong to moderate skin sensitiser;
- only limited data are available on eye and skin irritation;

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

- there is a lack of data on acute or repeated dose inhalation toxicity and repeated dose dermal toxicity;
- the overseas restrictions for use of this chemical in hair dyes state that the maximum concentration allowed in an oxidative hair dye substance is 1.5 % (after mixing with hydrogen peroxide); and
- that as many hair dye formulations come under Schedule 6 due to p-phenylenediamine content, inclusion in Schedule 6 with a cut-off is not likely to give an effective upper concentration limit for the chemical.

As a strong sensitiser, 4-amino-2-hydroxytoluene could be hazardous even below the maximum concentration of 1.5 % permitted under the EU Cosmetic Regulation. The appropriate parent Schedule is 5 or 6. Given the potential for induction and elicitation of sensitisation below the cut-off, the risk would be better controlled by inclusion of warning statements on the label of preparations containing the chemical below the cut-off. This is consistent with Schedule 6 entries for some other hair dye ingredients.

Delegate's reasons for referring this to the committee

The toxicological issues in this scheduling proposal are similar to those considered by the ACCS in November 2013 for 2-amino-5-ethyl-phenol and in July 2014 for o-aminophenol. The delegate's reasons for referring the current proposal for 4-amino-2-hydroxytoluene are similar, in that it is an ingredient in hair dyes and cosmetic products for dyeing eyebrows and eyelashes and it has the following toxicological issues: acute toxicity, mutagenicity and sensitisation potential. The NICNAS recommendation was for scheduling controls to restrict use in hair dye and other cosmetic preparations. Its use in cosmetics is restricted in various overseas regulations. ACCS advice is needed to determine the optimal scheduling actions to achieve the requested controls.

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 4-amino-2-hydroxytoluene (acute toxicity, mutagenicity and sensitisation potential) warrants stringent controls over use in cosmetics and consumer products?
- What weight should be given to the evidence of moderate to severe skin sensitisation potential? Does the data suggest a suitable cut-off for the sensitisation potential?
- In the light of insufficient information on carcinogenicity, what weight should be given to the range of positive (in vitro) and negative (in vivo) studies on genotoxicity?
- Does the ACCS consider that including 4-amino-2-hydroxytoluene in Schedules 6 ,7 or 10 is the best option for controlling its use in consumer products and cosmetics, including hair dyes and eyebrow/eyelash products? Should there be a cut-off to exempt at 1.5%, as suggested in the NICNAS report?
- If the ACCS recommends listing in Schedule 6, should exemptions apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- What name should be used for any schedule entry – 5-amino-2-methyl-phenol, 5-amino-o-cresol or 2-hydroxy-p-toluidine?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products?

Substance summary

Refer to the NICNAS IMAP report which is publicly available on the NICNAS website: NICNAS IMAP assessment ID 928.

Acute toxicity

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

Toxicity	Species	4-amino-2-hydroxytoluene	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	3600	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	>5000	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	Rabbit	Not irritant at concentrations up to 10 % (limited data)	N/A
Eye irritation	Rabbit	Not irritant at concentrations up to 2.5 %	N/A

Skin sensitisation

The chemical is considered to be a strong to moderate skin sensitiser, based on the following results from the NICNAS IMAP report.

Two LLNAs were conducted (OECD TG 429) in female CBA mice (n = five/concentration), using two different vehicles (first assay with water/acetone 1:1 mixed with olive oil at 4:1 and the second assay with dimethyl sulfoxide (DMSO)). All test concentrations of 0.5, 1.5, 3 and 5 % produced a stimulation index (SI) over three (3.2, 5.9, 5.3 and 9.4, respectively) in the first assay; only the 5 % concentration produced a SI over three (SI = 3.9) in the second assay. The positive control, para-phenylenediamine at a 1 % concentration, exhibited an SI of 31.2 in the first assay and 12.7 in the second. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3), which was calculated to be 0.44 % in the first assay and 3.4 % in the second, indicated a strong and moderate sensitising potential, respectively.

In another LLNA study (not validated by the NTP), BALB/c mice exposed to the chemical at concentrations of 0.625, 1.25, 2.5, 5 and 10 % (in acetone and olive oil) exhibited a significant increase of lymphocyte proliferation at 5 % and 10 % concentrations, but only the highest dose induced a three-fold increase. The chemical was reported to be weakly sensitising.

In an open epicutaneous test with albino guinea pigs, the chemical at a 3 % concentration (in a vehicle containing 2 % Natrosol 250HR, 2 % Tween 80, 0.05 % sodium sulfite, 82.95 % deionised water and 10 % isopropanol) induced positive reactions in 4/19 animals.

In a Magnusson Kligman study in female Hartley guinea pigs, the chemical was used at 1 % and 25 % in propylene glycol for intradermal and epidermal induction applications, respectively. Challenge with epidermal application of the chemical at a 25 % concentration produced a positive reaction in 4/10 guinea pigs.

Repeat-dose toxicity

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

Genotoxicity

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

Carcinogenicity

Based on the available genotoxicity data for the chemical and its N-acetylated metabolites, and information available from Quantitative Structure Activity Relationship (QSAR) modelling, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemical is not expected to have reproductive and developmental toxicity. However, some reproductive and developmental effects were reported at very high doses in rats (at 1000 mg/kg bw/d), probably due to severe maternal toxicity effects.

Public exposure

The chemical is reported to be used in permanent hair dye preparations in Australia. The chemical may also be in products to colour eyelashes.

Many countries, including New Zealand and the European Union, have restricted the use of this chemical in cosmetics. Following a safety evaluation, the SCCP (2006) concluded that the use of the chemical 'as an oxidative hair dye substance at a maximum concentration of 1.5 % in the finished cosmetic product (after mixing with hydrogen peroxide) does not pose a risk to the health of the consumer, apart from its sensitising potential'.

If the chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic N-nitrosamine compounds could be formed (SCCS, 2012b).

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

International regulations

The chemical is listed on the following registers:

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III Part 2—List of substances provisionally allowed;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: '(a) Hair dye substance in oxidative hair dye products; (b) Products intended for colouring eyelashes; For (a) and (b): After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 1.5%; (b) For professional use only; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

Scheduling status

4-amino-2-hydroxytoluene is not specifically scheduled.

Scheduling history

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

Public pre-meeting submissions

One public submission was received. The submission states that there are no objections to aligning the Australian scheduling with those in the EU. It also suggested 4-amino-2-hydroxytoluene should be cross-referenced to 5-amino-*o*-cresol and 4-amino-2-hydroxytoluene.

The public submissions are available at Public submission on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended a new Schedule 6 entry be created for 4-amino-2-hydroxytoluene with cut-offs for hair dye preparations containing 1.5% or less of the substance after mixing for use when the containers are labelled with the appropriate warning labels.

The committee also recommended Appendix E and F entries be created as follows:

Appendix E: Statements A and E1; and

Appendix F: Statement 28, part 1

The committee also recommended changing the name from its original reference of Phenol, 5-amino-2-methyl is 4-AMINO-2-HYDROXYTOLUENE.

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Hair dye, eyelash and eyebrow tinting products.
- Fits the criteria in Schedule 6: skin sensitiser.

Delegate's interim decision

Schedule 6—New Entry

4-AMINO-2-HYDROXYTOLUENE in hair dyes and eyebrow/eyelash colouring products **except**:

a) in hair dye preparations containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statements:

   KEEP OUT OF REACH OF CHILDREN, and

   WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

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

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statement:

   WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

   Written in letters not less than 1.5mm in height.

Appendix E, Part 1—New Entry

Poison	Standard Statement
4-AMINO-2-HYDROXYTOLUENE	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 – If in eyes wash out immediately with water

Appendix F, Part 1—New Entry

Poison	Warning Statement
4-AMINO-2-HYDROXYTOLUENE	28 - (Over) (Repeated) exposure may cause sensitisation/

Index—New Entry

5-AMINO-O-CRESOL see 4-AMINO-2-HYDROXYTOLUENE

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

The proposed implementation date is 1 June 2016.

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

The reasons for the interim decision comprised the following:

> 4-amino-2-hydroxytoluene is an ingredient of oxidative hair dyes. In common with other amine hair dye ingredients, there is a risk of skin/eye irritation and skin sensitisation. This risk has been managed for other oxidative hair dye ingredients by listing in Schedule 6, with 'reverse scheduling' provisions that exempt some preparations when labelled with appropriate warning statements. The delegate accepts ACCS advice that 4-amino-2-hydroxytoluene scheduling should be managed in the same way as previously scheduled hair dye ingredients.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

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

Public submissions on the interim decision

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

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

Delegate's final decision

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

2.11 2-amino-6-chloro-4-nitrophenol (Phenol, 2-amino-6-chloro-4-nitro)

Scheduling proposal

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

- In April 2015 the delegate received a request to consider creating a new entry for 2-amino-6-chloro-4-nitrophenol and its hydrochloride in Schedule 6 to include use in hair dyes with an appropriate cut-off.

Scheduling application

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

- A proposal to create a new entry for 2-amino-6-chloro-4-nitrophenol and its hydrochloride in Schedule 6 to include use in hair dyes with an appropriate cut-off.

The reasons for the request were:

- the chemicals have reported cosmetic use in permanent hair dye preparations in Australia
- the chemicals are strong to moderate skin sensitisers;
- only limited data are available on eye and skin irritation;
- there is a lack of data on acute or repeated dose inhalation toxicity; and
- the overseas restrictions for use of these chemicals in hair dyes state that the maximum concentration allowed in an oxidative hair dye substance is 2 % (after mixing with hydrogen peroxide) (SCCP, 2006). This concentration may be based on the lowest EC3 value calculated (0.68 %) for skin sensitisation of the parent base.

The appropriate parent Schedule is 5 or 6. Given the potential for induction and elicitation of sensitisation below the cut-off, the risk would be better controlled by inclusion of warning statements on the label of hair dye formulations containing the chemicals below the cut-off. This is consistent with Schedule 6 entries for some other hair dye ingredients.

Delegate's reasons for referring this to the committee

The toxicological issues in this scheduling proposal are similar to those considered by the ACCS in November 2013 for 2-amino-5-ethyl-phenol and in July 2014 for o-aminophenol. The delegate's reasons for referring the current proposal for 2-amino-6-chloro-4 nitro-phenol are similar, in that it is an ingredient in hair dyes and cosmetic products for dyeing eyebrows and eyelashes and it has the following toxicological issues: acute toxicity, mutagenicity and sensitisation potential. The NICNAS recommendation was for scheduling controls to restrict use in hair dye and other cosmetic

preparations. Its use in cosmetics is restricted in various overseas regulations. ACCS advice is needed to determine the optimal scheduling actions to achieve the requested controls.

The delegate asked the committee the following questions:

- Does the ACCS agree that the toxicological profile of 2-amino-5-chloro-4-nitro-phenol (primarily sensitisation potential) warrants appropriate controls over use in cosmetics and consumer products? Does the data suggest that 2% is a suitable cut-off for the sensitisation potential?
- Does the ACCS have concerns about the limited information available about mutagenic and/or carcinogenic potential? More stringent scheduling controls imposed on other aminophenolic oxidative dyes have generally been based on stronger evidence of mutagenicity. The NICNAS IMAP report points out that electron-withdrawing groups (Cl and nitro) on aminophenols tends to weaken their genotoxic potential.
- If the ACCS recommends listing in Schedule 6, should exemptions only apply when the product is labelled with appropriate warning statements, consistent with other oxidative hair dye ingredients with similar toxicological profiles?
- Which of the names in the NICNAS IMAP report should be used for any schedule entry? Would this substance be covered (as a derivative) by the current generic Schedule 6 entry for - NITROPHENOLS, ortho, meta and para except when separately specified in these schedules?
- Is there a need for specific entries in Appendices E & F to manage labelling of scheduled products? Note that there is a current Appendix F requirement for statements 1,4, and 8 for nitrophenols covered by the generic S6 entry.

Substance summary

Please refer to the NICNAS IMAP report available on the NICNAS website: NICNAS IMAP assessment ID 1078.

Acute toxicity

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

Toxicity	Species	2-amino-6-chloro-4-nitrophenol and/or its hydrochloride	SPF Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	Rabbit	Not irritant at concentrations up to 0.5 % (limited data)	N/A
Eye irritation	Rabbit	Not irritant at concentrations up to 2 %	N/A

Skin sensitisation

Based on the data available for the parent base from the NICNAS IMAP report, both chemicals are considered to be skin sensitisers.

Data are available for the parent base. In a local lymph node assay (LLNA) (OECD TG 429), groups of female CBA mice were topically treated with 25 µL of the chemical at 0, 0.5, 5 and 10 % concentrations (using two vehicles: DMSO and acetone/water/olive oil), once a day for three consecutive days. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated as 6.85 % with dimethyl sulfoxide (DMSO) and 0.68 % with acetone/water/olive oil. The EC3 of 0.68 % may be an overestimate as there was no clear dose response below the 10 % concentration. The chemical is considered to be a skin sensitiser.

Another LLNA study (OECD TG 429) calculated the EC3 as 2.2 %.

Repeat-dose toxicity

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

Genotoxicity

Based on the available data, the chemicals are not considered to be genotoxic.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the parent base and the salt. Based on the available genotoxicity data and information available from Quantitative Structure Activity Relationship (QSAR) modelling, the chemicals are not considered to be carcinogenic.

Reproductive and developmental toxicity

No reproductive toxicity data are available. Based on the data available for the parent base, both chemicals are not considered to have developmental toxicity.

Public exposure

2-amino-6-chloro-4-nitrophenol and its hydrochloride are reported to be used in semi-permanent hair dye preparations and the parent base is also reported to be used in permanent hair dye preparations in Australia.

New Zealand and the European Union have restricted the use of these chemicals in hair dye preparations to a maximum of 2 % concentration when applied directly to the hair.

If these chemicals are included in cosmetic products containing N-nitrosating agents, carcinogenic N-nitrosamine compounds could be formed.

Currently, there are no restrictions in Australia on using these chemicals in hair dyes. The skin sensitisation risk could be mitigated by implementing concentration limits for use in hair dyes.

International regulations

2-amino-6-chloro-4-nitrophenol and its hydrochloride are both listed on the following:

- EU Cosmetics Regulation 1223/2009 Annex III, part 1—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down. The restrictions include the following: for use as a hair dye substance in either oxidative or non-oxidative hair dye products; a maximum concentration of 2 % in ready-for-use preparations; and after mixing under oxidative conditions, the maximum concentration applied to hair must not exceed 2 %.

The parent base is listed on the following (Galleria Chemica):

- New Zealand Cosmetic Products Group Standard (2006)—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down. These restrictions and conditions are similar to the ones indicated above.

Scheduling status

2-amino-6-chloro-4-nitrophenol and its hydrochloride are not specifically scheduled.

Scheduling history

2-amino-6-chloro-4-nitrophenol or its hydrochloride have not been previously considered for scheduling; therefore, scheduling history is not available.

Public pre-meeting submissions

One public submission was received. The submission stated that for nitrophenols there is currently a S6 entry with no exemptions for preparations containing small quantities of the substances. The submission also stated that there were no objections to aligning Australian scheduling with those of the EU where there are exemptions for use in hair dyes in small quantities.

The public submissions are available at Public submissions on scheduling matters.

Summary of ACCS advice to the delegate

The committee recommended a new Schedule 6 entry be created for 2-amino-6-chloro-4-nitrophenol with cut-offs for hair dye preparations applied directly contains 2% or less of the substance and when the immediate container is labelled with the appropriate warning labels.

The committee also recommended Appendix E/F entries be created as follows:

Appendix E: Statements A and E1; and

Appendix F: Statement 28, part 1

The committee also recommended changing the name from its original reference of phenol, 2-amino-6-chloro-4-nitro is 2-AMINO-6-CHLORO-4-NITROPHENOL.

The committee recommended an implementation date of 1 February 2016.

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

The reasons for the recommendations comprised the following:

- Hair dye, eyelash and eyebrow tinting products.
- Fits the criteria in Schedule 6 as a skin sensitiser.

Delegate's interim decision

Schedule 6—New Entry

2-AMINO-6-CHLORO-4-NITROPHENOL in hair dye and eyebrow/eyelash colouring preparations, **except**:

a) in preparations containing 2 per cent or less of 2-amino-6-chloro-4-nitrophenol when applied directly to the hair, or containing 2 per cent or less of 2-amino-6-chloro-4-nitrophenol after mixing and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 2-amino-6-chloro-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

Written in letters not less than 1.5mm in height.

Appendix E, Part 1—New Entry

Poison	Standard Statement
2-AMINO-6-CHLORO-4-NITROPHENOL	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 – If in eyes wash out immediately with water

Appendix F, Part 1—New Entry

Poison	Warning Statement
2-AMINO-6-CHLORO-4-NITROPHENOL	28 - (Over) (Repeated) exposure may cause sensitisation.

The delegate considered the relevant matters under subsection 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 the substance.

The proposed implementation date is 1 June 2016. A later implementation date is proposed to allow for an orderly process of re-labelling of products already on the market.

The reasons for the interim decision comprised the following:

2-amino-6-chloro-4-nitrophenol is an ingredient of oxidative hair dyes. In common with other amine hair dye ingredients, there is a risk of skin/eye irritation and skin sensitisation. This risk has been managed for other oxidative hair dye ingredients by listing in Schedule 6, with 'reverse scheduling' provisions that exempt some preparations when labelled with appropriate warning statements. The delegate accepts ACCS advice that 2-amino-6-chloro-4-nitrophenol scheduling should be managed in the same way as previously scheduled hair dye ingredients.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;

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

Public submissions on the interim decision

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

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

Delegate's final decision

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

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

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

3. Agriculture and veterinary chemicals

Summary of delegate's final decisions

Substance	Final Decision
Afoxolaner and Milbemycin oxime	***Schedule 5—Amend Entries*** AFOXOLANER in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit a) for the treatment and prevention of flea infestations and control of ticks in dogs; or b) for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs, when combined with milbemycin oxime. ***Schedule 5—Amend Entries*** MILBEMYCIN OXIME a) for the prophylaxis of heartworm in dogs and cats; or b) for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs, when combined with afoxolaner, in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit. *Implementation date: 1 February 2016*
BLAD (banda de *Lupinus albus* doce)	***Appendix B—New Entry*** BLAD (banda de *Lupinus albus* doce) Part 1: Reasons for entry a – low toxicity Part 2: Areas of Use 1.3 - fungicide *Implementation date: 1 February 2016*
Bixafen	***Schedule 5—New Entry*** BIXAFEN *Implementation date: 1 February 2016*

3.1 Afoxolaner and Milbemycin oxime

Scheduling proposal

Applicant proposal:

The applicant has applied for a reconsideration of the scheduling entry for milbemycin oxime, proposing designated as a Schedule 5 product. The applicant did not provide specific justification or argument to support their request to amend the scheduling listing for milbemycin oxime.

OCS proposal:

In August 2015 the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for registration of a new veterinary medicine, requested that the delegate consider amending the entry for afoxolaner in Schedule 5. The recommended amendment is as follows:

> Afoxolaner for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit.

OCS considerations

The basis for the OCS recommendation is that:

The proposed product containing 18.75 mg/g afoxolaner (and 3.75 mg/g milbemycin oxime) meets the APVMA data guidelines for domestic use products as;

- it is expected to have low acute oral and acute dermal toxicity and is considered to have low skin and eye irritancy and is not sensitising to the skin;
- it is considered that repeated use of the product will pose a low risk to the user; and
- it is considered that the proposed formulation and packaging in conjunction with recommended safety directions will further mitigate any risk to users.

The previous Scheduling consideration with regards to afoxolaner active constituent is also relevant to the current Scheduling consideration. That is that afoxolaner: was listed in Schedule 5 as a delegate only decision in April 2014. The decision to list the active in Schedule 5 was due to its low toxicity profile which was consistent with the SPF for listing in Schedule 5 and because the treatment instruction were sufficiently clear that pet owners should be able to manage the required dosage regimen without a veterinarian's oversight.

There is no evidence of an altered toxicokinetic profile or additional toxicity when afoxolaner is administered in a chewable tablet formulation at a higher rate than currently scheduled (2.5 mg/kg bw equivalent to a maximum 150 mg in the highest dose chewable) or when in a novel combination with milbemycin oxime. Studies in dogs conducted with the formulated product and submitted by the applicant indicate that there is no significant change in toxicokinetic parameters for afoxolaner when administered in combination with milbemycin oxime in a chewable formulation. The applicant provided:

- toxicokinetic studies which showed comparable toxicokinetic parameters for afoxolaner when administered alone and in combination with milbemycin oxime.
- target animal species safety studies indicating no additional toxicity up to 5 X the recommended dose when afoxolaner is administered in combination with milbemycin oxime.

An acute toxicity study with the technical forms of afoxolaner and milbemycin in combination which showed minor clinical signs (decreased defaecation, decreased size of faeces, stained urogenital and anogenital region, red material on nose or forelimb) at a dose of 1273 mg/kg bw (approximating to 1000 mg/kg bw afoxolaner and 200 mg/kg bw milbemycin oxime). In an accidental poisoning

scenario, the likely maximum ingested dose by a child (entire 6-pack of the largest chewable size) would be 900 mg of afoxolaner (and 180 mg of milbemycin oxime), equivalent to 81.8 mg/kg bw afoxolaner (and 16.4 mg/kg bw milbemycin oxime) for an 11 kg child. Considering the estimated acute oral LD_{50} of the product (LD_{50} is low i.e. >>5000 mg/kg bw), the lack of evidence of increased risk when the active constituents are administered in combination and the type of product packaging proposed is considered child resistant, it is likely that there is an adequate margin in this scenario between the maximally ingested dose and the real acute oral LD_{50}.

The OCS notes that the product meets the APVMA data guidelines for domestic use products as they are expected to have low acute oral and acute dermal toxicity and will be considered to have low skin and eye irritancy and will not be sensitising to the skin. It is also considered that repeated use of the product should pose a low risk to the user. Further, it is considered that the proposed formulation and packaging in conjunction with recommended safety directions will further mitigate the risk to users.

Consideration of the SPF criteria and application of the cascading principles outlined in the SPF indicates that the active constituent afoxolaner when administered for use in a chewable tablet formulation meets the scheduling criteria for Schedule 5 for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit as:

- it is non-corrosive,
- it has low toxicity,
- it has a low health hazard from repeated use,
- it does not require specialised equipment for safe use,
- there is no evidence of a significantly altered toxicokinetic profile or additional toxicity when afoxolaner is administered in a novel combination with milbemycin oxime;
- the risk mitigation measures proposed for the product (i.e. appropriate labelling to inform the consumer of safety measures to apply during handling or use and child resistant packaging) will assist to protect the user from undue harm; and
- it has a low potential for causing harm.

Substance summary

Toxicity of afoxolaner

Afoxolaner, a member of the isoxazoline family, binds at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA)[14], thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors[15].

[14] 4-Azolylphenyl isoxazoline insecticides acting at the GABA gated chloride channel. Lahm et al March 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/23566518
[15] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=111643

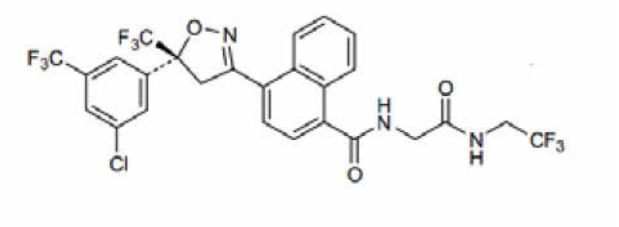

Figure 1: Structure of afoxolaner.

Toxicity endpoint	Species	Afoxolaner
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	LD50 > 1,000 (no deaths)
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD50 >2000 mg/kg bw
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	n/a	No study submitted
Skin irritation	Rabbits	Non-irritating
Eye irritation	Rabbit	Moderate
Skin sensitisation LLNA	Mice	Non-sensitiser

Short-term toxicity

Target/critical effect	Reduced food consumption and body weight loss/reduced body weight gain (rats and rabbits)
Lowest relevant oral NOEL (mg/kg bw/d)	10 (90-d oral, rat): based on reduced food consumption and body weight gain, numerous secondary effects on haematology, serum chemistry, urine specific gravity and volume at 50 mg/kg bw/d
Lowest relevant dermal NOEL (mg/kg bw/d)	10 (56-day, rat; limited regulatory value)
Lowest relevant inhalation NOEC (mg/m^3)	No inhalational study submitted
Genotoxicity	Non-genotoxic

Long-term toxicity and carcinogenicity

Target/critical effect	No long-term studies submitted
Carcinogenicity	No studies provided, though afoxolaner, was not genotoxic in *in vitro* and *in vivo* genotoxicity studies
Reproductive toxicity Reproduction target/critical effect	Reproductive parameters unaffected by treatment. Not a reproductive toxicant in one-generation study. Evidence of treatment-related toxicity at 20 mg/kg bw/d (reduced body weight gain and food consumption, reduced mean number of implantation sites and pups born live and litter size). Foetal death (during lactation period) and lower foetal weights.
Lowest relevant reproductive NOEL (mg/kg bw/d)	Parental NOEL: 5 (rats), Reproductive NOEL: 5 (rats) Offspring NOEL: 5 (rats)
Developmental toxicity	Development unaffected by treatment. Not a developmental toxicant in rats and rabbits
Developmental target/critical effect	Evidence of treatment-related toxicity at 10 mg/kg bw/d (reduced food consumption and body weight gain) in dams
Lowest relevant developmental NOEL (mg/kg bw/d)	Maternal NOEL: 3 (rats) Foetal NOEL: 10 (rats)

Toxicity of the product

No acute studies were submitted on the formulated product. Information available indicates the product, containing 18.75 mg/g afoxolaner and 3.75 mg/g milbemycin oxime is formulated with excipients of generally low toxicity. The expected acute toxicity was extrapolated from data on the excipients.

Toxicity end point	Product
Oral	Low toxicity
Dermal	Low toxicity
Inhalational	Low toxicity**
Skin irritation	Slight irritant**
Eye irritation	Slight irritant**
Skin sensitisation	Not sensitising

* based on the toxicological profile of all ingredients in the product

** expected to be low exposure by this route, due to nature of formulation (chewable tablet) and use pattern

Observation in humans

No information was provided.

Public exposure

The product will be administered primarily by pet owners.

Potential users should be warned that accidental ingestion of afoxolaner can be harmful. Furthermore, while repeated dosing is unlikely to occur accidentally or inadvertently, there is no PPE that can be used to prevent such repeat exposure. The inclusion of the statement "*Do not swallow*" in the recommended safety directions is considered to appropriately reflect the risks associated with cumulative exposure in this case. Noting the formulation type and the intended domestic use of the product, the inclusion of the safety directions "*Do not open inner pouch until ready for use*" and "*Wash hands after use*" are also considered appropriate.

International regulations

No information was provided.

Scheduling status

Afoxolaner is listed in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for the treatment and prevention of flea infestations and control of ticks in dogs in oral divided preparations each containing 140 mg or less of afoxolaner per dosage unit.

Scheduling history

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 which was consistent with the SPF for listing in Schedule 5.

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.

The delegate also considered whether a Schedule 4 listing for afoxolaner could be more appropriate, providing for oversight of treatment by a veterinarian. The delegate indicated that because the treatment instructions are sufficiently clear that pet owners should be able to manage the required dosage regimen without a veterinarian's oversight.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[16];
- Other relevant information.

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

Delegate's final decision

Schedule 5—Amend Entries

AFOXOLANER in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit

a) for the treatment and prevention of flea infestations and control of ticks in dogs; or

b) for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs, when combined with milbemycin oxime.

MILBEMYCIN OXIME

a) for the prophylaxis of heartworm in dogs and cats; or

b) for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs, when combined with afoxolaner, in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit

While this is a re-scheduling application, and the SPF suggests that such applications be referred to an Advisory Committee, in effect the amendment sought is simply to extend the range of indications for a product where the two active ingredients are already included in Schedule 5 for the indications sought.

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

The implementation date is 1 February 2016.

3.2 BLAD (banda de *Lupinus albus* doce)

Scheduling proposal

In August 2015, the APVMA has referred the proposal to create a new entry for BLAD in Appendix B for use as a biofungicide on various crops and ornamentals for consideration by the delegate for inclusion in the SUSMP.

The reasons for the request are:

- the substance is proposed to be used in a biofungicidal product
- the product contains 20 per cent of the active substance BLAD
- the product is expected to have low acute oral, dermal and inhalational toxicity
- the product is expected to be a mild eye irritant, a slight skin irritant and is not a skin sensitiser
- the US EPA regulations for use of this substance was an exemption from the requirement of a tolerance for residues of BLAD in or on food commodities when applied as a fungicide and used in accordance with label directions and good agricultural practices. This was due to reasonable certainty that no harm to the population will result from aggregate exposure to residues of BLAD.

The toxicology data and other information on the product provided and considered during this assessment justify the Safety Directions established. The information on the product provided and the additional information considered in this assessment was used to evaluate the additional use patterns. The proposed use of the product will not be an undue health hazard to humans according to the criteria stipulated in Section 14 of the *Ag/Vet Code Act of 1994*.

Substance summary

The applicant has applied for approval of a new active constituent (BLAD) and registration of the associated product and approval of the product label (Category 2 Application). The applicant has submitted Part 3 (toxicology) and Part 6 (OHS) data for assessment. The APVMA has requested an assessment of the toxicity and OHS of the active and the product and recommendations (if any), for health standards, scheduling and/or labelling e.g. safety directions.

The active constituent is a polypeptide termed BLAD (from the Portuguese 'banda de *Lupinus albus* doce' or band from sweet *Lupinus albus*). BLAD is a naturally-occurring seed storage protein, which accumulates exclusively in the cotyledons of Lupinus species (for example, *Lupinus albus*), between days four and twelve after the onset of germination. It is a 20 kDa polypeptide of β-conglutin, or characterized as a fragment of the amino acid sequence of β-conglutin. The β-conglutin protein is classified as a 7S globulin which is part of the broader family of cupin proteins, which provides a major nitrogen source for germination of the developing plant.

The product is a non-systemic biofungicide applied as a foliar spray with claimed strong antifungal activities both for prevention and control.

The biochemical pesticide is manufactured as an end-use product with neither isolation of the technical grade active constituent nor formation of a manufacturing product (MUP). The product contains 20% of the active ingredient, BLAD (pure active constituent). The product is intended to be registered as a new biofungicide for the control and suppression of powdery mildew, botrytis, anthracnose and other fungal diseases in various crops and ornamentals and can be used as a foliar spray alone, in alternating spray programs or in tank mixes with other registered pesticides using conventional spray equipment.

Hazard characterisation

The active ingredient and the formulated product fungicide are effectively equivalent formulations. While the product contains added adjuvants which comprise 14% of the formulation, there is removal of the aqueous solvent during manufacture so that the concentration of the BLAD active constituent remains unchanged at 20% (w/w) for both the TGAC and the formulated product. On this basis the toxicity profile of BLAD and the fungicide are considered identical as the only difference between them is a change in the concentration of inert non-reactive ingredients (described as a commonly used surfactant and an antifoam).

The mechanism of fungicidal action by BLAD is an important determinant of its lack of mammalian toxicity. BLAD, used as a fungicide, is a naturally occurring 20 kilo Dalton (kDa) polypeptide of β-conglutin formed during days 4 to 12 of the germination process of the flowering plant, sweet lupines (*Lupinus albus*). It is also characterized as a fragment of the amino acid sequence of β-conglutin and the main storage protein in sweet lupines providing a major nitrogen source for germination of the developing plant. *Lupines albus*, commonly known as white or sweet lupine or lupin, is a member of the genus Lupinus in the family of Fabaceae. *Lupines albus* contains the full range of essential amino acids and for hundreds of years has been widely cultivated worldwide, thus sweet lupines have a long history of safe use in human and livestock consumption without any adverse effects. BLAD is directly extracted from the flowering plant, sweet lupines. It has a dark brown colour with a sweet odour and is stated to be 60% biodegradable within 14 days after application. Physicochemical information is provided at Appendix 1.

The product is a non-systemic biofungicide with claimed strong antifungal activities making it useful for prevention and control of fungal infections such as powdery mildew and grey mould on fruit, vegetable and ornamental crops and blossom blight on stone fruit. The non-toxic mode of action is described as binding very strongly to chitin in fungal cell walls, inhibiting any fungal growth. The active ingredient degrades chitin by catalysing the removal of the N-acetyl-D-glucosamine terminal chitin monomers, and destroying the fungal cells.

Toxicity profile

Acute toxicity

As noted, the TGAC and product can be considered equivalent in toxicity. The acute toxicity of the fungicide in laboratory animals was low via the oral, dermal, and inhalation routes of exposure. The fungicide is mildly irritating to the skin and eyes but is not a dermal sensitizer.

Subchronic toxicity

The applicant has provided copies of waiver requests made to the United States Environmental Protection Agency (USEPA) seeking exemption from the need to provide various studies as follows: 90-Day Oral, 90-Day Dermal, 90-Day Inhalation, Prenatal Development, Bacterial Reverse Mutation Test, In vitro Mammalian Chromosome Aberration. The arguments provided by the applicant were uniformly that: the active ingredient is a naturally occurring product with a history as a food and feed item (sweet lupines), it has very low acute toxicity by any route, is rapidly biodegraded (60% is biodegradable within 14 days in the environment) and its use according to label directions will lead to negligible subchronic exposure. These arguments were considered reasonable and have been accepted by other regulatory agencies.

Reproductive, developmental and chronic toxicity and carcinogenicity

No long term toxicology or carcinogenicity studies have been conducted on BLAD and the applicant seeks a waiver to the requirements for these studies using the same arguments as for the lack of subchronic studies, i.e. that the active ingredient is a naturally occurring product with a history as a food and feed item (sweet lupines), it has very low acute toxicity by any route, is rapidly biodegraded and its use according to label directions will lead to negligible chronic exposure. In particular, dietary risks to humans are considered negligible, based on the lack of dietary toxicological endpoints for BLAD and its nontoxic mode of action as a fungicide. These arguments were considered reasonable and have been accepted by other regulatory agencies.

Additionally, both USEPA and the Canadian Pest Management Regulatory Agency (PMRA) reviewed studies pertaining to the chronic exposure of lupine products. Ballester et al (1984) reported a study of the potential reproductive and developmental toxicity of lupin protein. In that study, sweet lupine flour was fed for 9 months to two generations of rats (F1 and F2) at a level that provided 20% dietary protein. The diets were supplemented with 0.2% DL-methionine. The lupine diet had no effect on the general condition, mortality or behaviour of the animals. The growth rate of males fed sweet lupine was significantly higher than that of the controls. Haematological parameters and tests of liver function were normal in all treatment groups. At autopsy there were no significant changes in the weight of the heart, kidney, spleen, brain and gonads but the relative weight of the liver of lupine-fed rats was significantly lower than that in the controls. However, there were no histological changes in these livers. The lupin protein was reported to have no effect on either fertility or reproductive parameters in any of the generations.

Chronic life-time studies (i.e. 700 and 800 days) in rats fed sweet lupin seeds did not reveal any evidence of carcinogenicity in lupin-treated animals, and no signs of toxicity or decreases in body weight occurred (Grant et al, 19933; Grant et al 19954).

Allergenicity

Food Standards Australia New Zealand (FSANZ) has expressed concern about possible food allergies arising from consumption of lupins but has yet to undertake regulatory action. PMRA notes increasing reports of allergy resulting from the use of lupine derived seed products in prepared foods, indicating some concern that the germinated sweet lupine seed extract in the product may also be allergenic. Based on informatics, susceptibility to protease digestion, and estimates of dietary intake, BLAD polypeptide is expected to be of low potential to cause allergic reactions and to cross-react with known allergens from other legumes, such as peanuts and soybean. PMRA notes that the proteins (conglutins) in lupine seed that are responsible for allergic reactions in sensitive individuals are not present.

As no chronic studies have been conducted on BLAD no appropriate toxicology endpoints have been established for deriving an ADI or ARfD. Given the minimal exposure during short-term use and the expected lack of residues on crops there is no need for these health guideline values.

Selection of a NOEL for OHS Risk Assessment

Occupational exposure to the product is characterized as short-term and is predominately by the dermal and inhalation routes as it is mildly irritating to the eyes and to the skin. Dermal absorption of BLAD polypeptide is not expected.

International regulations

The USEPA has approved and the PMRA is about to approve products containing BLAD.

USA EPA: In March 2013, the US EPA established an exemption from the requirement of a tolerance for residues of BLAD in or on all food commodities when applied as a fungicide and used in accordance with label directions and good agricultural practices. In establishing this exemption from the requirement for a pesticide chemical residue in or on a food, the USEPA stated that:

> "*All of the data requirements to support a tolerance exemption were fulfilled by the applicant. EPA concluded that the data are acceptable and no additional data are required. No acute, subchronic, or chronic toxicity endpoints were identified in guideline studies or in data obtained from open technical literature. Moreover, BLAD is not a mutagen, and is not a developmental toxicant. There are no known effects on endocrine systems via oral, dermal, or inhalation exposure.*"

Additionally:

> "*BLAD has the following properties and characteristics: BLAD is used in human and animal nutrition as a food and feed item; and ii. BLAD has a nontoxic mode of action against fungal pests and 60% is biodegradable within 14 days in the environment, thereby minimizing any potential for toxic risk, such that there is no concern for potential exposure.*"

In April 2013, The U.S. EPA granted registration for the Food Machinery Corporation (FMC) end use product Fracture containing BLAD as a fungicide for use on grapes, stone fruit, strawberries and tomatoes.

The Pest Management Regulatory Agency of Canada published a Proposed Registration Decision (PRD) for BLAD on 6 February 2015. This PRD states that:

> "*BLAD polypeptide is unlikely to affect human health when it is used according to label directions. Potential exposure to BLAD polypeptide may occur when handling and applying the end-use product. In laboratory animals, the acute toxicity of the end-use product containing BLAD polypeptide, was low via the oral, dermal, and inhalation routes of exposure. Product is mildly irritating to the skin and eyes; …and is not a dermal sensitizer. …A request to bridge acute toxicity data from the end-use product to the technical grade active ingredient was considered to be acceptable. The active ingredient, BLAD polypeptide, was considered to be of low acute toxicity via the oral, dermal, and inhalation routes of exposure. …BLAD polypeptide is not expected to cause effects in developing young or to cause damage to genetic material when used according to the label instructions. …Occupational risks are not of concern when used according to the proposed label directions, which include protective measures.*"

Scheduling status

BLAD is not specifically scheduled.

Scheduling history

BLAD has not been previously considered for scheduling therefore scheduling history is not available.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's final decision

Appendix B—New Entry

BLAD (banda de Lupinus albus doce)

Part 1: Reasons for entry a – low toxicity

Part 2: Areas of Use 1.3 - fungicide

Reasons for delegate's decision

The low toxicity profile of this product does not suggest any need to list it any of the Schedules of the Poisons Standard. This is reinforced by the fact that systemic exposure to this polypeptide has occurred through food consumption of sweet lupins. Accordingly, the delegate accepts the recommendation of the OCS evaluation report that scheduling is not required, and that a listing in Appendix B be developed to signify this decision.

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

The implementation date is 1 February 2016.

3.3 Bixafen

Scheduling proposal

In September 2015, the Office of Chemical Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to approve a new active constituent bixafen, recommends that the Delegate consider creating a new entry for bixafen in Schedule 5 of the SUSMP.

Agency/applicant's considerations

The reasons for the request are:

> A data package seeking approval of the new active constituent bixafen, a member of the carboxamide fungicide class of chemicals belonging to the sub-class of the pyrazole-carboxamides, a succinate dehydrogenase inhibitor of fungal pathogens was received. As a new chemical for AgVet use, it will require consideration for SUSMP listing prior to final registration of products. Currently the proposed product attached to this application is for agricultural use.

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

Substance summary

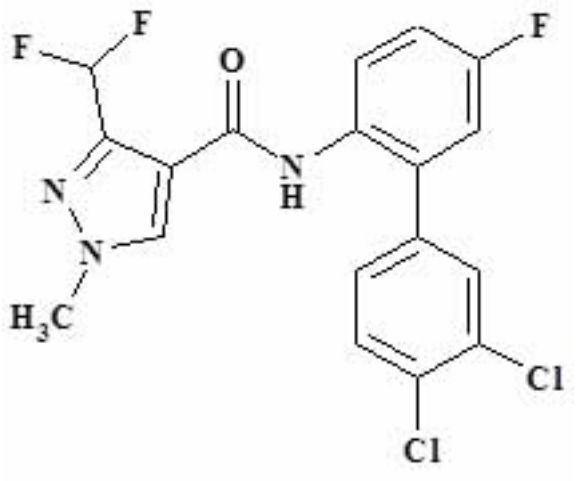

Figure 1. Structure of Bixafen (BYF 00587)

Acute toxicity

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

Toxicity	Species	Bixafen	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Wistar Rat	>2000 (no deaths)	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Wistar Rat	>2000 (no deaths)	Appendix B
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Wistar Rat	>5383 (no deaths)	Appendix B
Skin irritation	NZW rabbit	Non-irritant	Appendix B
Eye irritation	NZW rabbit	Non-irritant	Appendix B
Skin sensitisation (LLNA method)	NMRI mouse	No determination possible not of regulatory quality	Not applicable

Repeat-dose toxicity

The systemic toxicity of bixafen in dietary studies consisted primarily of decreases in body weight and body weight gain, liver toxicity such as increased liver weight and centrilobular hepatocellular hypertrophy with associated clinical chemistry changes, and thyroid effects (e.g. follicular cell hypertrophy) generally seen at higher dose levels. This systemic toxicity profile was observed in short-term, subchronic and chronic toxicity studies in rats, mice and dogs, with the available data indicating that rats and mice were equally sensitive. A mechanistic study indicated that hepatotoxicity may be due to induction of both phase I and II hepatic enzymes.

Mutagenicity/Genotoxicity

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

Carcinogenicity

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

Reproductive toxicity potential

In a dietary two generation study in rats, parental systemic toxicity was seen at the top (2500 ppm) and mid dose (400 ppm) level. At the top dose decreased body weight (5%-6% decrease seen in dams of both generations throughout gestation), decreased body weight gain (15%-18% decrease in body weight gain in dams of both generations throughout gestation and lactation), and increased liver, spleen, thyroid, thymus (females only) and kidney (males only) weights were noted in both genders. At the mid dose male liver weight was increased (P_0 only) while female liver weights were increased in all doses in the P_1 generation. Liver hypertrophy was also sharply increased in high dose rats of both generations and sexes. Reproductive findings were not affected by treatment. In offspring, decreased pup body weight (8%-12% decrease seen in pups of both generations on day 21) and pup body-weight gain, and decreased spleen, thymus (F1 only) and brain weights were also seen at the top dose level. However, OCS considers that the observed effects in offspring were a secondary non-specific consequence of maternal toxicity. Bixafen is not considered to be a reproductive toxicant.

Developmental toxicity potential

No evidence of a developmental toxicity potential was seen in an oral (gavage) developmental toxicity study in rats at the mid and high dose levels that produced marked maternal toxicity (e.g. body weight gain was 42% lower during the dosing period compared to controls at the high dose), with foetal weights also decreased at mid and high dose levels. Maternal body weight gains were decreased at the high dose during the treatment period and liver weights were increased in both the mid and high dose dams.

In an oral (gavage) developmental toxicity study in rabbits maternal body weight gains were decreased at the high dose during the treatment period and liver weights were increased in both the mid and high dose dams, along an increased incidence of visceral and skeletal findings at the high dose were seen. While these findings were outside of the historical control range they were seen in the presence of marked maternal toxicity (e.g. body weight gain was reduced (↓74%) at several time intervals between GD 6 and 26 and overall (GD 6 to 29; ↓59%) as well as reduced foetal weights (↓6% combined). Thus, bixafen was not considered to be a developmental toxicant in rabbits as the observed skeletal findings in foetuses were considered a secondary non-specific consequence of marked maternal toxicity.

Other toxicology endpoints

No evidence of neurotoxicity was seen in acute and repeat dose studies however, this was not investigated independently in standard neurotoxicity studies.

Bixafen was not investigated for immunotoxic potential.

Observation in humans

No information was provided.

Public exposure

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

International regulations

The European Food Safety Authority (via the United Kingdom as the rapporteur member state lead for the evaluation) published a peer review of the pesticide risk assessment of the active substance bixafen in November 2012 and products containing bixafen are registered in the United Kingdom.

Scheduling status

Bixafen is not specifically scheduled.

Scheduling history

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

Delegate's consideration

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[18];
- Other relevant information.

Delegate's final decision

Schedule 5—New Entry

BIXAFEN

Reasons for delegate's decision

The toxicology profile for bixafen is relatively straightforward, and its low toxicity profile suggests possible listing in Appendix B. However, the OCS evaluation report draws attention to the submitted LLNA sensitisation test was non-compliant. Despite a compliant LLNA test on the combination product with prothioconazole that was negative for sensitisation potential, the OCS evaluation recommends listing in Schedule 5 as a cautionary measure, and the sponsor has accepted that recommendation.

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

The implementation date is 1 February 2016.

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