Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health and invitation for the public to provide further comment for the ACCS Meeting #14 and the ACCS/ACMS #11

5–6 August 2015

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

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

The delegate’s interim decisions and reasons relate to:

• scheduling proposals initially referred to the August 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#14);

• scheduling proposals initially referred to the August 2015 Joint meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee of Medicines Scheduling (ACCS/ACMS #11)

Pre-meeting public notice

A ‘pre-meeting’ public notice inviting submissions on the scheduling proposals referred to the expert advisory committee was published on 28th May 2015 at Consultation: Invitation for public comment – ACCS meeting, August 2015.

Redacted versions of these public submissions received in response to this invitation were published in October 2015 at Public submissions on scheduling matters.

Interim decisions

This notice provides the interim decisions of the delegate, the reasons for those decisions and invites further submissions from the applicant and parties who made valid submissions in response to the original invitations for submissions. Further submissions must be relevant to the proposed amendment, must address a matter mentioned in section 52E of the Therapeutic Goods Act 1989 and be received by the closing date 15th October 2015.

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

Please note that all valid submissions received on or before the closing date will be published following removal of confidential information. It is up to the person making the submissions to
highlight any information which they wish to be considered as confidential. Material claimed to be commercial-in-confidence will be considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the *Scheduling Policy Framework for Medicines and Chemicals* (SPF, July 2015), issued by the Australian Health Ministers’ Advisory Council (AHMAC). The SPF is accessible at [Scheduling Policy Framework](#).

Persons making submissions are strongly encouraged to lodge submissions in electronic format (word or unsecured PDF preferred) via the email address Chemicals.Scheduling@health.gov.au.

The closing date for further submissions is **15 October 2015**.

### 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: [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 [www.health.gov.au](http://www.health.gov.au)
## Glossary

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<tr>
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<th>Name</th>
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<tr>
<td>ACCC</td>
<td>Australian Competition and Consumer Commission</td>
</tr>
<tr>
<td>ACCS</td>
<td>Advisory Committee on Chemicals Scheduling</td>
</tr>
<tr>
<td>ACMS</td>
<td>Advisory Committee on Medicines Scheduling</td>
</tr>
<tr>
<td>ADI</td>
<td>Acceptable daily intake</td>
</tr>
<tr>
<td>AHMAC</td>
<td>Australian Health Ministers' Advisory Council</td>
</tr>
<tr>
<td>AICS</td>
<td>Australian Inventory of Chemical Substances</td>
</tr>
<tr>
<td>APVMA</td>
<td>Australian Pesticides and Veterinary Medicines Authority</td>
</tr>
<tr>
<td>ARfD</td>
<td>Acute reference dose</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstract Service</td>
</tr>
<tr>
<td>DPSC</td>
<td>Drugs and poisons Scheduling Committee</td>
</tr>
<tr>
<td>FAISD</td>
<td>First Aid Instructions and Safety Directions</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
</tr>
<tr>
<td>FSANZ</td>
<td>Food Standards Australia New Zealand</td>
</tr>
<tr>
<td>GHS</td>
<td>Globally Harmonised System for Classification and Labelling of Chemicals</td>
</tr>
<tr>
<td>IMAP</td>
<td>Inventory Multi-tiered Assessment Prioritisation</td>
</tr>
<tr>
<td>ISO</td>
<td>International Standards Organization</td>
</tr>
<tr>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>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.</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>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.</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Lowest observed adverse effect level</td>
</tr>
<tr>
<td>LOEL</td>
<td>Lowest observed effect level</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Name</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>MOE</td>
<td>Margins Of Exposure</td>
</tr>
<tr>
<td>NDPSC</td>
<td>National Drugs and poisons Scheduling Committee</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NICNAS</td>
<td>National Industrial Chemicals Notification &amp; Assessment Scheme</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No observed adverse effect level</td>
</tr>
<tr>
<td>NOEL</td>
<td>No observed effect level</td>
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<tr>
<td>NOHSC</td>
<td>National Occupational Health &amp; Safety Commission</td>
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<tr>
<td>OCS</td>
<td>Office of Chemical Safety</td>
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<tr>
<td>PEC</td>
<td>Priority existing chemical</td>
</tr>
<tr>
<td>PHED</td>
<td>Pesticide Handler Exposure Data [i.e. PHED Surrogate Exposure Guide]</td>
</tr>
<tr>
<td>SPF</td>
<td>Scheduling Policy Framework for Medicines and Chemicals [Scheduling Policy Framework]</td>
</tr>
<tr>
<td>SUSMP</td>
<td>Standard for the Uniform Scheduling of Medicines and Poisons</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1.8 QUINOLINE, 5,6,7,8-TETRAHYDRO-8-(1-METHYLPROPYL)

1.9 PHENOL 4-AMINO-3-METHYL (4-AMINO-M-CRESOL)

1.10 PHENOL 5-AMINO-2-METHYL (4-AMINO-2-HYDROXYTOLUENE)

1.11 PHENOL 2-AMINO-6-CHLORO-4-NITRO (2-AMINO-6-CHLORO-4-NITROPHENOL)

## Part B. Scheduling proposals referred to the August 2015 Joint meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling (ACCS/ACMS #11)

2.1 METHYLISOTHIAZOLINONE (MIT)

2.2 METHYLCHLOROISOTHIAZOLINONE (MCI)
Part A - Scheduling proposals referred to the August 2015 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#14)

1.1 CYCLOPROPYLMETHYL, 3-HEXENOATE

Scheduling proposal

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

The reasons for the request were:

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

Delegate’s reasons for referring this to the committee

The 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 to one other fragrance chemical (4,4-dimethyl-1-cyclohexene-1 propanal) was to list it is Schedule 6, with exempt cut-offs at 0.1% to 1% for various cosmetic and other product types. The different ACCS advice appears to be related to the severity of the toxicity potential of the pure compound, with 4,4-dimethyl-1-cyclohexene-1 propanal recommended a Schedule 6 listing because of the severity of the skin/eye irritancy potential and sensitization potential.

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the toxicological profile of 3-Hexenoic acid, cyclopropylmethyl ester 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 3-Hexenoic acid, cyclopropylmethyl ester 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**

![Chemical structure](image)

**Acute toxicity**

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>3-Hexenoic acid, cyclopropylmethyl ester</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD50 (mg/kg bw)</td>
<td>Rat</td>
<td>300-2000</td>
<td>Consistent with Schedule 6</td>
</tr>
<tr>
<td>Acute dermal toxicity LD50 (mg/kg bw)</td>
<td>Rat</td>
<td>&gt; 2000</td>
<td>None</td>
</tr>
<tr>
<td>Acute inhalation toxicity LC50 (mg/L/4h)</td>
<td>Rat</td>
<td>&gt; 5.18</td>
<td>None</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Slightly irritating</td>
<td>None</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Slightly irritating</td>
<td>None</td>
</tr>
<tr>
<td>Skin sensitisation (Local lymph node assay)</td>
<td>Mouse</td>
<td>No evidence of sensitisation</td>
<td>None</td>
</tr>
</tbody>
</table>

**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 $\leq 0.05\%$ 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**

3-Hexenoic acid, cyclopropylmethyl ester is not specifically scheduled.

**Scheduling history**

3-Hexenoic acid, cyclopropylmethyl ester 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**

3-Hexenoic acid, cyclopropylmethyl ester except:

(a) when used in fine fragrances at a concentration of 0.05% or less;

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

(c) when used in household products at a concentration of 0.05% or less.

**Reasons for the suggested cut-offs**

As stated above, the NICNAS recommended usage concentrations of 0.05% in fine fragrances, 0.03% in other cosmetic products and 0.05% 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 3-Hexenoic acid, cyclopropylmethyl. 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 submission is available at Scheduling Submissions

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% 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%. The risk to public health at very low concentrations is minimal

Delegate’s considerations

The delegate considered the following in regards to this proposal:

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

Delegate’s interim decision

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

Not Applicable

1.2 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.

The reasons for the request were:

- The applicant has submitted a data package 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 agricultural use, it will require consideration by the delegate for SUSMP listing prior to registration of products containing this active constituent.
- Proposed products attached to the 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. The delegate decided to seek ACCS advice on the scheduling proposal.

The delegate asked the ACCS the following questions:

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

Acute toxicity

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Bicyclopyrone</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD50 (mg/kg bw)</td>
<td>Rat (HanRcc:WIST (SPF))</td>
<td>&gt;5000 (no deaths)</td>
<td>Not Scheduled</td>
</tr>
<tr>
<td>Acute dermal toxicity LD50 (mg/kg bw)</td>
<td>Rat (HanRcc:WIST (SPF))</td>
<td>&gt;5000 (no deaths)</td>
<td>Not Scheduled</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC50 (mg/m3/4h)</td>
<td>Rat (HanRcc:WIST (SPF))</td>
<td>&gt;5.2 (no deaths)</td>
<td>Not Scheduled</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit (NZW)</td>
<td>Non-irritant</td>
<td>Not Scheduled</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit (NZW)</td>
<td>Slight irritant</td>
<td>Schedule 5</td>
</tr>
<tr>
<td>Skin sensitisation (LLNA)</td>
<td>Mouse (CBA/Ca CruBR)</td>
<td>Not sensitising</td>
<td>Not Scheduled</td>
</tr>
</tbody>
</table>

An abridged overview of the OCS report is included below.

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 urinary 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 (OMIM 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 (OMIM 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 T₃ and T₄ (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 findings 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 T₄ being shorter in rodents (12 – 24 hours) than in humans (5 – 9 days), there is serum T₄ binding with thyroxine-binding globulin in humans which is absent in rodents (meaning there is more unbound T4 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 50 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

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Reasons for scheduling delegate’s interim decision and invitation for further comment
1 October 2015
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**


**Scheduling status**

Bicyclopyrone is not currently scheduled.

**Scheduling history**

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

**Pre-meeting public 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. These abnormalities occurred at background rates in the animals tested and therefore the substance is not warranted to be classified as a developmental toxicant.

The OCS submitted a reply to a submission and highlighted that the 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 a Schedule 6 listing with a cut-off to Schedule 5 at 20% and less be put in place for bicyclopyrone.

The public submissions are available at [Scheduling Submissions](#)
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 foetotoxicity or potential for developmental toxicity consistent with Schedule 6.

Delegate’s considerations

The delegate considered the following in regards to this proposal:

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

Delegate’s interim decision

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.

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

Schedule entry

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 recommends an implementation date of 1 February 2016.

1.3 CLITORIA TERNATEA EXTRACT

Scheduling proposal

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 APVMA to approve a new biological active constituent.

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 and is not currently listed in the SUSMP.

- Consideration of the SPF criteria and application of the cascading principles outlined in the SPF indicates that the active constituent *Clitoria ternatea* Extract meets the scheduling factors for Schedule 5, with a moderate eye irritation potential.

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 applicant has requested listing in Appendix B (i.e. not scheduled). Note that the SUSMP is quite explicit that an applicant’s application to create an Appendix B entry will not be accepted. In order to resolve the differences between the applicant and the OCS as to the most appropriate scheduling action, the delegate referred for advice from the ACCS.

The delegate asked the ACCS 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.

**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.

**Proposed wording for the schedule entry**

**Schedule 5 – New Entry**

*CLITORIA TERNATEA EXTRACT*

**Pre-meeting public 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 submission is available at [Scheduling Submissions](#)

**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**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Standard Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clitoria ternatea</em> Extract</td>
<td>B – use pattern restricts hazard and area of use</td>
</tr>
</tbody>
</table>

**Appendix B, Part 2 – Areas of use**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Standard Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clitoria ternatea</em> Extract</td>
<td>1.2 – Insecticide</td>
</tr>
</tbody>
</table>

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 considerations**

The delegate considered the following in regards to this proposal:
Delegate’s interim decision

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.

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

Schedule entry

Appendix B – New Entry

*CLITORIA TERNATEA* EXTRACT.

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

The delegate recommends an implementation date of 1 February 2016.

1.4 CYCLOPENTANE, ALPHA,ALPHA-DIMETHYLPROANOL

Scheduling proposal

In April 2015, the NICNAS, under its New Chemicals assessment programme, referred a proposal to create a new entry for cyclopentanepropanol, α,α-dimethyl- in Schedule 6 when used in cosmetic and household products, except when used in accordance with the NICNAS recommended usage concentrations.

The reasons for the request were:

- The chemical 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, an MOE of 171 was estimated.

The chemical has been early listed on to the 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 ACCS has previously considered a number of fragrance chemicals referred from the NICNAS. For chemicals with a low toxicity profile and likely to be present at quite low concentrations in products in the retail market, the ACCS has advised that there is insufficient public health risk to warrant inclusion in a schedule of the 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 to one other fragrance chemical (4,4-dimethyl-1-cyclohexene-1 propanal) was to list it is Schedule 6, with exempt cut-offs at 0.1% to 1% for various cosmetic and other product types. The different ACCS advice appears to be related to the severity of the toxicity potential of the pure compound, with 4,4-dimethyl-1-cyclohexene-1 propanal recommended a Schedule 6 listing because of the severity of the skin/eye irritancy potential and sensitization potential.

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the toxicological profile of 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, α,α-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

Refer to the New Chemical assessment report available on the NICNAS website:
**Acute toxicity**

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Cyclopentanopropanol, α,α-dimethyl-</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>&gt; 2,000</td>
<td>None</td>
</tr>
<tr>
<td>Acute dermal toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>&gt; 2,000</td>
<td>None</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC₅₀ (mg/m³/4h)</td>
<td>Not provided</td>
<td>Not provided</td>
<td>-</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Slight irritant</td>
<td>Consistent with Schedule 5</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Irritant</td>
<td>Consistent with Schedule 6</td>
</tr>
<tr>
<td>Skin sensitisation (Local lymph node assay)</td>
<td>Mouse</td>
<td>No evidence of sensitisation</td>
<td>None</td>
</tr>
</tbody>
</table>

**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, α,α-dimethyl- is not specifically scheduled.

**Scheduling history**

Cyclopentanepropanol, α,α-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.

**Pre-meeting public submissions**

No public submissions were 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 CYCLOPENTANEPROPA NOL, 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 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;
- Other relevant information.

**Delegate’s interim decision**

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 to not schedule this substance.

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

**Schedule entry**

**Schedule 5—New Entry**

CYCLOPENTANEPROPANOL, ALPHA,ALPHA-DIMETHYL-, except in preparations containing 1 per cent or less of cyclopentanepropanol, alpha,alpha-dimethyl-

The delegate recommends an implementation date of 1 February 2016.

### 1.5 HYDRAMETHYLNON

**Scheduling proposal**

In March 2014 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.

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 and currently listed in Schedules 5 and 6. Since there is disagreement between the recommendations of the OCS evaluation report, and the applicant’s responses, the delegate requests advice from the ACCS.

The delegate asked the ACCS the following questions:

- The key issue considered by the NDPSC in 1996 was whether a brief exposure to a granular bait containing hydramethylnon 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

Acute toxicity

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Hydramethylnon</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD50 (mg/kg bw)</td>
<td>Rat</td>
<td>Low (LD_{50}=1131 mg/kg bw)</td>
<td>Schedule 6</td>
</tr>
<tr>
<td>Acute dermal toxicity LD50 (mg/kg bw)</td>
<td>Rabbit</td>
<td>Low (LD_{50}&gt;15 g/kg bw)</td>
<td>Schedule 5</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC50 (mg/m³/4h)</td>
<td>rats</td>
<td>Low (LC_{50}&gt;600 mg/m³ no deaths)</td>
<td>Schedule 6</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Skin sensitisation (Local lymph node assay)</td>
<td>Guinea pigs</td>
<td>Non-sensitiser</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Toxicity end point</th>
<th>Hydramethylnon</th>
<th>Pyriproxyfen</th>
<th>Synergy Ant Bait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (mg/kg bw)</td>
<td>Low (LD_{50}=1131 mg/kg bd/w)</td>
<td>Low (LD_{50}&gt;5000 mg/kg bd/w)</td>
<td>Low (LD_{50}&gt;2000 mg/kg bd/w no deaths)</td>
</tr>
<tr>
<td>Dermal (mg/kg bw)</td>
<td>Low (LD_{50}&gt;15 g/kg bd/w)</td>
<td>Low (LD_{50}&gt;2000 mg/kg bd/w)</td>
<td>Low (LD_{50}&gt;2000 mg/kg bd/w no deaths)</td>
</tr>
<tr>
<td>Inhalational (mg/m³)</td>
<td>Low (LC₅₀&gt;600 mg/m³, no deaths)</td>
<td>Low (LC₅₀&gt;1300 mg/m³)</td>
<td>Low *</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------</td>
<td>-----------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Slight</td>
<td>Nil</td>
<td>Non irritant</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Moderate</td>
<td>Slight</td>
<td>Non-irritant*</td>
</tr>
<tr>
<td>Skin sensitisation</td>
<td>Nil</td>
<td>Nil</td>
<td>Non sensitiser</td>
</tr>
</tbody>
</table>

*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. Glomerulonephritis 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 (F₁ onwards) were not retained at ≥100 ppm due to lack of offspring, the subsequent F₁ and F₂ 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 F₀ generation was markedly reduced. At 100 ppm, mating indices were higher than controls during both mating periods, however, none of the females delivered an F₁a litter and only 6 females delivered an F₁b 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 F0 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 F0 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 F1 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 F1 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 F1 litters (from F0 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 F1 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 F0 and 1/30 F1 males at 75 ppm and in 1/29 F0 rats at 50 ppm (none in F1 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
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, alopecia, 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

Please refer to OCS human health risk assessment report Attachment E.

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 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 pyriproxyfen.

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 submissions were received.

**Summary of ACCS advice to the delegate**

The committee recommended the current scheduling remains appropriate.

**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;
- Other relevant information.

**Delegate’s interim decision**

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 labyrinth. 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.

**Schedule entry**

N/A.

**1.6 MOMFLUOROTHIN**

**Scheduling proposal**

In May 2015, the OCS, based on an application made to the APVMA to register a new active ingredient, requested that the delegate consider creating a new entry for momfluorothrin in Schedule 6 of the SUSMP.

The reasons for the request were:

- The was a submission seeking approval of the 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 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 momfluothrin 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 ACCS 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 monfluothrin is consistent with listing in Schedule 6, based on the sex difference in LD50 (>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

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{N} & \quad \text{C} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{F} & \quad \text{F} \\
\text{C} & \quad \text{O} \\
\text{F} & \quad \text{F} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

Acute toxicity

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Momfluorothrin</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>300 &lt; LD₅₀ &lt; 2000 mg/kg bw for females</td>
<td>Schedule 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LD₅₀ &gt; 2000 mg/kg bw for males</td>
<td></td>
</tr>
<tr>
<td>Acute dermal toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>LD₅₀ &gt;2000 mg/kg bw</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC₅₀ (mg/m³/4h)</td>
<td>Rat</td>
<td>LC₅₀ &gt;2030 mg/m³, 4-hour exposure, one death</td>
<td>N/A</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Not irritating</td>
<td>N/A</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Slight irritant</td>
<td>Schedule 5</td>
</tr>
<tr>
<td>Skin sensitisation (Maximisation test)</td>
<td>Guinea Pig</td>
<td>Not sensitising</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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 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 submissions were received.

**Summary of ACCS advice to the delegate**

The committee recommended a new Schedule 6 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 that the substance meets criteria for Schedule 6 due to acute oral toxicity.

**Delegate’s considerations**

The delegate considered the following in regards to this proposal:

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

**Delegate’s interim decision**

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 LD$_{50}$ 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.

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

**Schedule entry**

**Schedule 6—New Entry**

MOMFLUOROTHIRN

The delegate recommends an implementation date of 1 February 2016.

### 1.7 CARCINOGENIC AMINES (AZODYES)

**Scheduling proposal**

In April 2015, the NICNAS under its IMAP programme, referred the a proposal create a new entry for various dyes that could release selected carcinogenic amines (listed on AICS) and/or the aromatic amine precursors in Schedule 7 or Appendix C.

*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 ACCS 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 IMAP human health Tier II assessment reports for

- Dyes that could release selected carcinogenic amines (listed on AICS)

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 (\textit{p}-aminoazobenzene-based); Solvent Red 19 (\textit{p}-aminoazobenzene-based); Disperse Yellow 7 (CAS No. 6300-37-4) (\textit{p}-aminoazobenzene-based); Solvent Red 24 (\textit{o}-anisidine-based); and Orange Oil SS (\textit{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 \textit{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 (\textit{p}-aminoazobenzene; \textit{o}-anisidine; \textit{o}-toluidine; 2-4-toluenediamine; \textit{o}-aminoazotoluene; 4-chloro-\textit{o}-toluidine; and \textit{p}-chloroaniline) are classified as hazardous (Category 2 carcinogenic substance) with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe work Australia). The chemical 5-Nitro-\textit{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 \textit{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.

\textbf{Public exposure}

\textit{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:

- 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 DYSES 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-diaminophenylazo)[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-naphthalenylazo)[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 has 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 - Amendment**
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.

**Pre-meeting public 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.

The public submission is available at [Scheduling Submissions](#).

**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 considerations**

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors;
- Other relevant information.
Delegate’s interim decision

The 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’.

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.

Schedule entry

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 recommends an implementation date of 1 February 2016.

1.8 QUINOLINE, 5,6,7,8-TETRAHYDRO-8-(1-METHYLPROPYL)

Scheduling proposal

In April 2015, the NICNAS, under its New Chemicals assessment programme, referred a proposal to create a new entry for quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)- in Schedule
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, an 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 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 ACCS 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

Refer to the New Chemical assessment report available on the NICNAS website:
http://www.nicnas.gov.au/__data/assets/word_doc/0019/13555/LTD-1737-FR-Final.docx

Acute toxicity

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Quinoline, 5,6,7,8-tetrahydro-8-(1-methylpropyl)-</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>&gt; 2000</td>
<td>None</td>
</tr>
<tr>
<td>Acute dermal toxicity LD₅₀ (mg/kg bw)</td>
<td>Not provided</td>
<td>Not provided</td>
<td>-</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC₅₀ (mg/m³/4h)</td>
<td>Not provided</td>
<td>Not provided</td>
<td>-</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Irritating</td>
<td>Consistent with S5</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Slightly irritating</td>
<td>Consistent with S5</td>
</tr>
<tr>
<td>Skin sensitisation (Local lymph node assay)</td>
<td>Mouse</td>
<td>Evidence of sensitisation (EC₃ = 6.1%)</td>
<td>Consistent with S6</td>
</tr>
</tbody>
</table>

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 submission was received.

Summary of ACCS advice to the delegate

The committee recommended the substance does not require 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;
- Other relevant information.

**Delegate’s interim decision**

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.

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

**Schedule entry**

N/A

1.9 PHENOL 4-AMINO-3-METHYL (4-AMINO-M-CRESOL)

**Scheduling proposal**

In February 2015, the NICNAS, under its IMAP programme, referred the following proposal to create a new entry for phenol, 4-amino-3-methyl in Schedule 5 to include use in hair dyes and eyelash colouring products with an appropriate cut-off to the delegate for scheduling consideration.

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).

**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-3-methyl-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 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

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Reasons for scheduling delegate’s interim decision and invitation for further comment

1 October 2015
various overseas regulations. ACCS advice is needed to determine the optimal scheduling actions to achieve the requested controls.

The delegate asked the ACCS the following questions:

- Does the ACCS agree that the toxicological profile of 4-amino-3-methyl-phenol (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-3-methyl-phenol 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-3-methyl-phenol, 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**


**Acute toxicity**

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Phenol, 5-amino-2-methyl</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>870 mg/kg bw</td>
<td>Schedule 6</td>
</tr>
<tr>
<td>Acute dermal toxicity LD₅₀ (mg/kg bw)</td>
<td>N/A</td>
<td>No data</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC₅₀ (mg/m³/4h)</td>
<td>N/A</td>
<td>No data</td>
<td>N/A</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Guinea pig</td>
<td>Not irritant at concentrations up to 3 % (limited data)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
**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:

- 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

Phenol, 4-amino-3-methyl is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

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


Summary of ACCS advice to the delegate

The committee recommended a new Schedule 6 entry be created for 4-amino-\textit{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-\textit{m}-cresol are to be created.
Appendix E, Part 1 – New Entry

<table>
<thead>
<tr>
<th>Poison</th>
<th>Standard Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-amino-m-cresol</td>
<td>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</td>
</tr>
</tbody>
</table>

Appendix F, Part 1 – New Entry

<table>
<thead>
<tr>
<th>Poison</th>
<th>Warning Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-amino-m-cresol</td>
<td>28 - (Over) (Repeated) exposure may cause sensitisation.</td>
</tr>
</tbody>
</table>

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 considerations

The delegate considered the following in regards to this proposal:

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

Delegate’s interim decision

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.

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

**Schedule entry**

**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**

<table>
<thead>
<tr>
<th>Poison</th>
<th>Standard Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-AMINO-M-CRESOL</td>
<td>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</td>
</tr>
</tbody>
</table>
Appendix F, Part 1 – New Entry

<table>
<thead>
<tr>
<th>Poison</th>
<th>Warning Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-AMINO-M-CRESOL</td>
<td>28 - (Over) (Repeated) exposure may cause sensitisation.</td>
</tr>
</tbody>
</table>

The delegate recommends an implementation date of 1 June 2016.

1.10 PHENOL 5-AMINO-2-METHYL (4-AMINO-2-HYDROXYTOLUENE)

Scheduling proposal

In February 2015, the NICNAS, under its IMAP programme, referred a proposal to create a new entry for phenol, 5-amino-2-methyl in Schedule 6 to include use in hair dyes and eyelash colouring products to the delegate for scheduling consideration.

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;
- 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, phenol, 5-amino-2-methyl 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 5-amino-2-methyl-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 ACCS the following questions:

- Does the ACCS agree that the toxicological profile of 5-amino-2-methyl-phenol (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 5-amino-2-methyl-phenol 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**


**Acute toxicity**

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Phenol, 5-amino-2-methyl</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD₅₀ (mg/kg bw)</td>
<td>Rat</td>
<td>3600</td>
<td>Schedule 5</td>
</tr>
<tr>
<td>Acute dermal toxicity LD₅₀ (mg/kg bw)</td>
<td>Rabbit</td>
<td>&gt;5000</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC₅₀ (mg/m3/4h)</td>
<td>N/A</td>
<td>No data</td>
<td>N/A</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Not irritant at concentrations up to 10 % (limited data)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### 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:

- 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

 Phenol, 5-amino-2-methyl is not specifically scheduled.
Scheduling history

Phenol, 5-amino-2-methyl has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One public submission was received. The submission stated 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.


Summary of ACCS advice to the delegate

The ACCS 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/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 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;
Delegate’s interim decision

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.

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

Schedule entry

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% 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% 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.
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 recommends an implementation date of 1 June 2016.

**1.11 PHENOL 2-AMINO-6-CHLORO-4-NITRO (2-AMINO-6-CHLORO-4-NITROPHENOL)**

**Scheduling proposal**

In February 2015, the NICNAS, under its IMAP programme, referred a proposal to create a new entry for phenol, 2-amino-6-chloro-4-nitro and its hydrochloride in Schedule 6 to include use in hair dyes with an appropriate cut-off to the delegate for scheduling consideration.

*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 ACCS 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**


**Acute toxicity**

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Phenol, 2-amino-6-chloro-4-nitro and/or its hydrochloride</th>
<th>SPF Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity LD50 (mg/kg bw)</td>
<td>Rat</td>
<td>&gt;2000</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----</td>
<td>------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Acute dermal toxicity LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg bw)</td>
<td>N/A</td>
<td>No data</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute inhalational toxicity LC&lt;sub&gt;50&lt;/sub&gt; (mg/m³/4h)</td>
<td>N/A</td>
<td>No data</td>
<td>N/A</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Not irritant at concentrations up to 0.5 % (limited data)</td>
<td>N/A</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Not irritant at concentrations up to 2 %</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**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 sensitizer.

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**

Phenol, 2-amino-6-chloro-4-nitro 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**

Phenol, 2-amino-6-chloro-4-nitro 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**

Phenol, 2-amino-6-chloro-4-nitro and its hydrochloride are not specifically scheduled.

**Scheduling history**

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

**Pre-meeting public submissions**

One public submission was received. The submission stated that for nitrophenols there is currently a Schedule 6 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.

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 considerations

The delegate considered the following in regards to this proposal:

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

Delegate’s interim decision

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.

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.
Schedule entry

Schedule 6 – New Entry

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

a) in preparations containing 2% or less of 2-amino-6-chloro-4-nitrophenol when applied directly to the hair, or containing 2% 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% or less of 4-amino-\textit{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

<table>
<thead>
<tr>
<th>Poison</th>
<th>Standard Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-amino-6-chloro-4-nitrophenol</td>
<td>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</td>
</tr>
</tbody>
</table>

Appendix F, Part 1 – New Entry

<table>
<thead>
<tr>
<th>Poison</th>
<th>Warning Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-amino-6-chloro-4-nitrophenol</td>
<td>28 - (Over) (Repeated) exposure may cause sensitisation.</td>
</tr>
</tbody>
</table>
The delegate recommends an implementation date of 1 June 2016.

**Part B. Scheduling proposals referred to the August 2015 Joint meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling (ACCS/ACMS #11)**

### 2.1 METHYLISOTHIAZOLINONE (MIT)

**Scheduling proposal**

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

- creating a new entry in an appropriate schedule for cosmetic/personal care preparations containing methylisothiazolinone; and
- an exemption from scheduling for preparations with low concentrations of methylisothiazolinone.

**Delegates’ reasons for referring this to the committee**

The delegate asked the committee the following questions:

- Scheduling of methylisothiazolinone was referred to the July 2014 meeting of the ACCS. Skin sensitisation potential was identified as the key toxicological issue, driving towards listing in Schedule 6 according to SPF criteria. At that time, the ACCS was aware that the EU SCCS and US CIR had considered possible thresholds for leave-on and rinse-off cosmetics containing methylisothiazolinone, below which the risk of skin sensitisation was considered to be acceptable. Both authorities appeared to reach different views on the sensitisation thresholds, and the ACCS advised waiting for a final decision from the US CIR before it could advise to the delegate on possible exemption cut-off(s) from a Schedule 6 entry. The US CIR published its final report in October 2014. The ACCS/ACMS is asked to advise on whether to adopt either the US CIR or EU SCCS sensitisation thresholds as an exemption cut-off from a new Schedule 6 entry for methylisothiazolinone.

- Alternatively, does the ACCS/ACMS support NICNAS advice that Schedule 6 controls are insufficient to protect the public and that consideration be given to listing in Appendix C (Schedule 10) with appropriate exemption cut-offs?

- Noting that the US CIR has specified that the 100ppm (0.01%) threshold is only suitable for rinse-off cosmetic products, and that a cut-off for leave-on cosmetic products has not been specified, other than that it be based on a product-by-product quantitative risk assessment, the ACCS is asked to advise on whether the EU SCCS proposal for a 15ppm (0.0015%) for rinse-off cosmetics is a more appropriate general cut-off from Schedule 6.

- Does the ACCS/ACMS advise that any schedule listing for methylisothiazolinone be specific for cosmetic products, as outlined in the NICNAS report? Should different...
thresholds be proposed for products that are not intended to be directly applied to skin (e.g. cleaning products, deodorisers, antimicrobial gels and sprays)?

- To what extent should the estimates of sensitisation potential derived from animal tests (LLNA and Buehler test) suggest a higher sensitisation threshold than the conclusions of the CIR and SCCS?

- Noting that methylisothiazolinone is used at comparable concentrations in some therapeutic goods, but notably in sunscreen products that are directly applied to the skin, does the ACCS/ACMS advise that a schedule entry should specifically exempt such therapeutic goods or should they be subjected to the same exemption cut-offs as cosmetics?

- Noting that there have been a significant number of reports of allergies associated with the use of methylisothiazolinone in cosmetic and consumer products. It was designated as ‘contact allergen-of-the-year’ in 2013 by the US Contact Dermatitis Society and there have been Australian case reports of contact dermatitis associated with its use in ‘wet wipes’. What weight should be given to the apparent lack of adverse reaction reports associated with its use in therapeutic goods?

- What regulatory impact might be expected in relation to registered AgVet products, given APVMA advice that the maximum concentration of MIT is of the order of 0.1-0.2%?

**Substance summary**

**Toxicokinetics**

Toxicokinetic studies in rats using the chemical and its analogue (CAS No. 55965-84-9) show that it is readily absorbed and metabolised. The major metabolic products of the chemical are N-methyl malonamic acid (NMMA) and the 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propionamide. These studies did not report accumulation of the chemical or its metabolites in tissues. It is widely distributed to all tissues in the body, with the highest level seen in the liver and lowest in the bone. The chemical is eliminated within 24 hours through urine > bile > faeces. In an in vitro human skin absorption study conducted in accordance with OECD Test Guideline (TG) 428, aqueous solutions of products containing the chemical were applied by occlusion for 24 hours at doses of 52.2, 104.3 or 313 µg/mL. Potential systemic bioavailability was estimated as a maximum of 75.5 % of the applied dose (SCCS, 2009).

**Acute Toxicity**

**Oral**

The chemical had high acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats (Crl:CD®BR strain) was 209 mg/kg bw (235 for male and 183 mg/kg bw for female rats). The chemical (99.7 %) was administered as a single dose through gavage at concentrations of 75, 150, 180, 225 and 300 mg/kg bw. Observed sub-lethal effects included passivity, ataxia, scant or no faeces, mucus in faeces, yellow or brown stained anogenital area, red-stained muzzle and/or lacrimation. Additionally, at necropsy reddened intestines and/or stomach mucosa, reddened glandular portion of the stomach, and distended stomachs were observed (CIR, 2010; SCCNFP, 2003).
Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia).

**Dermal**

The chemical had high acute toxicity in animal tests following dermal exposure. The median lethal dose (LD50) in rats (Crl:CD®BR strain) was 242 mg/kg bw for both sexes. The chemical (97.5 %) was administered undiluted at a single 24-hour occluded topical application on shaved intact skin. Observed sub-lethal effects included decrease in body weight in both sexes at higher dose groups (200 mg/kg and above). Local effects included blanching, oedema, erythema, desiccation, darkened or reddened areas, scabs, eschar, and/or sloughing (CIR, 2010).

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia).

**Inhalation**

The chemical had high acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC50) for aerosol in rats (Crl:CD®BR strain, 6 animals/group) after four-hour exposure was 0.11 mg/L. The necropsy showed signs of slight to severe redness in all lobes of the lung in all treatment groups (CIR, 2010).

In another study, the LC50 in rats (Crl:CD®BR strain, 5 animals/group) after four-hour aerosol exposure was reported at 0.33 mg/L. Observed sub-lethal effects included body weight reduction in females at higher dose groups (0.25 mg/kg and above). Signs of pale and/or reddened lungs, distended intestines, and/or wet muzzles were observed at necropsy (CIR, 2010).

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Very toxic by inhalation’ (T; R26) in HSIS (Safe Work Australia).

**Corrosivity**

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Causes burns’ (R34) in HSIS (Safe Work Australia).

The chemical was applied undiluted as a single semi-occluded application of 0.5 mL to shaved intact skin of New Zealand White rabbits for three minutes, one hour, and four hours. The three-minute exposure resulted in a very slight to well-defined erythema through to day seven and slight oedema at 1- and 48-hours observations. At 1 and 4 hour exposures to the chemical, skin irritation indicative of corrosivity (concave eschar) was observed on days 7 and 14, respectively (CIR, 2010; SCCNFP, 2003). In an in vitro study with skin constructs, exposure to 1.7 % of the chemical for three or 60 minutes was not corrosive to the skin. However, the chemical was corrosive at higher concentration of 51.1 % at an exposure period of 60 minutes (CIR, 2010).

**Eye Irritation**

The chemical is recommended for classification as corrosive. It is expected that undiluted chemical will be severely damaging to the eyes.
The chemical (undiluted) was found to be an irritant in a bovine cornea study measuring opacity and permeability. Eye irritation studies using formulations containing the chemical at 100 ppm (body lotion, shampoo and sunscreen) were found non-irritating (CIR, 2010).

**Skin Sensitisation**

The chemical produced skin sensitisation effects in several animal and human studies. Although the potency of these effects varied across the studies, skin sensitisation was sufficiently noted across all the studies to support the classification (refer to Recommendation section) (SCCS, 2009; CIR, 2010; Lundov et al., 2011; Yazar et al., 2011; Boyapati et al., 2013; Cahill et al., 2014; SCCS, 2013; Lammintausta et al., 2014).

Methylisothiazolinone, in combination with methylchloroisothiazolinone (MCI) in a ratio of 1:3, has been used in industrial and consumer products as a preservative since the beginning of the 1980s. The first cases of contact allergy caused by these chemicals were published in 1985. Although MCI has been considered a more potent sensitisier than MIT, this chemical is still classified as a strong sensitisier. As a result of the sensitising potential of these chemicals, the maximum permitted concentration in the EU of the mixed preservative in cosmetics in the ratio of 1:3 (MI:MCI) is 15 ppm (0.0015 %); the allowed concentration of MIT in the mixture is 3.75 ppm. Following a review of the safety of MIT, the chemical was allowed in cosmetic products in the EU at a maximum concentration of 100 ppm in 2005 (see Restrictions) (SCCNFP, 2003; Lundov et al., 2011). The CIR expert panel recommended that the United States cosmetic manufacturers use the chemicals at the same concentrations as allowed in the EU (CIR, 2010).

Following its approval for use as a preservative in cosmetic products in 2005 at a maximum concentration of 100 ppm, several reports have indicated the emergence of the issue of contact allergy to the chemical (see Sensitisation: observation in humans). The permitted use of the chemical at 100 ppm in cosmetic products is approximately 25-fold the permitted concentration of the chemical in the MI/MCI combination (3.75 ppm MIT in 15 ppm of MI/MCI).

The chemical, in a combination with MCI (1:3 ratio), is also used as a preservative in industrial products and there are no restrictions on the use of this chemical in industrial products. The chemical-induced occupational contact allergy and dermatitis were also reported after contact with wall covering glue and in a paint factory (Lundov et al., 2011; Boyapati et al., 2013; SCCS, 2013).

Although several reports on the sensitisation potential of the mixture (MI:MCI) are available in animals, the most comprehensive studies conducted on the chemical (MI) are reported below.

The potential for MIT to cause skin sensitisation was investigated in an OECD Test Guideline (TG) 406 study (Buehler test). In this study, four groups of Hartley guinea pigs (five/sex/group) were treated with the chemical in the form of 6 hours' induction with three doses each week for 3.5 weeks under an occlusive condition. The chemical was administered at 0.4 mL/dose containing concentrations of 1000, 5000, 15000 and 30000 ppm suspended in distilled water on shaved intact skin. The animals were allowed to rest for two weeks before the challenge application. During the challenge phase, the animals were patched with the chemical at doses 1000, 5000, or 15000 ppm in distilled water. The treated animals were monitored for erythema.
for 24 or 48 hours following the application. Appropriate controls were also used in this study. The results showed no erythema reactions in the non-induced control animals at any challenge concentration. However, incidences of erythema were observed in animals induced and challenged with the chemical at 1000 ppm or higher (Burnett et al., 2010; SCCS, 2013).

In another study (maximisation test), 60 female Hartley guinea pigs received six intradermal injections containing induction doses of 500 ppm or 800 ppm of the chemical. After a week, the treated animals were given a single 24-hour topical exposure to 0.1 mL of the chemical under occlusive conditions. The animals were challenged with 500 ppm or 800 ppm after two weeks and were evaluated for reactions at 24 and 48 hour periods. The animals were also subjected to rechallenge with 1000 ppm. The results showed that 550 ppm did not cause dermal reactions. Only one reaction was noted at 800 ppm dose challenge after the 48-hour observation. During the rechallenge, less than 30 % of the animals displayed grade one erythema. Based on these results, the chemical was not considered a sensitiser at concentrations up to 800 ppm (Burnett et al., 2010).

Furthermore, several mouse local lymph node assay (LLNA) studies have reported evidence suggesting that the chemical is a potential skin sensitiser. In one study, female CBA/Ca mice were treated with the chemical (19.7 % purity in water) at the concentrations of 0.049, 0.099, 0.197, 0.493, 0.985 % in acetone and olive oil (4:1; v/v) and also at the concentrations of 0.99, 1.97, 4.93, 9.85 % in propylene glycol (PG). The induction phase consisted of applying the chemical, positive controls (formaldehyde, glutaraldehyde, MCI/MIT mixture) or vehicles over the ears (25 µL/ear) for three consecutive days (days one, two and three). After two rest days, the proliferation of lymphocytes in the lymph node draining the application site was measured by incorporating tritiated methyl thymidine (day six) for five hours. A linear interpolation of the dose response data was used to estimate concentrations required to induce stimulation indices (SI) of 3, relative to concurrent vehicle-treated controls (the EC3 value). The EC3 values of 0.4 and 2.2 % were calculated for the chemical for acetone and olive oil (4:1; v/v) and PG solutions, respectively. It was concluded that the chemical has strong sensitising potential, with potency being comparable to that of the formaldehyde although much lower than the mixture of the chemical with MCI in 1:3 ratio. Similar findings were noted in another study, indicating that the chemical is a sensitiser at concentrations greater than 0.76 % in acetone/olive oil (4:1) with a reported EC3 value of 0.86 % (SCCS, 2013).

Overall, these data suggest that the chemical is a potential skin sensitiser.

Observation in humans

Contact allergy to the chemical and the mixed preservative (MI:MCI) has been commonly reported following its approval for use in cosmetics in 2005. Increased incidence of clinical sensitisation to MIT was more evident following the introduction of patch test for MIT alone. The prevalence of sensitisation increased from 1.94 % of all dermatological clinic patients in 2009 to 6.02% in 2012 in Germany. This increase was mainly stated to be driven by female patients aged≥40 years, patients with face dermatitis, and the use of cosmetics. Additionally, the chemical was named the 2013 "Contact Allergen of the Year" by the American Contact Dermatitis Society, indicating increased incidence of the chemical-induced contact dermatitis (Cahill et al., 2014).
Painters, beauticians, and patients with ano-genital dermatitis were identified as being potentially at risk for sensitisation to the chemical (Lundov et al., 2011; Uter et al., 2013; Gameiro et al., 2014; Lammintausta et al., 2014).

In a series of repeat insult patch tests (RIPT) in human volunteers, exposure to the chemical at doses 200, 300, 400, 500, or 600 ppm did not cause dermal sensitisation (CIR, 2010; Burnett et al., 2010). Conversely, cases of allergic contact dermatitis were also reported in patients who had come into contact with coolant solutions containing biocides and those who were exposed to paint additives containing 7-10% of the chemical. In addition, a lowest eliciting dose of 1.47 µg of the chemical (49 ppm) was observed in a sensitisation studies conducted in 11 MI-allergic patients (CIR, 2010).

The chemical has been reported to be an emerging and important allergen in both cosmetic and occupational settings in Australia. Baby wipes and facial wipes containing the chemical were reported to be an important cause of hand dermatitis in carers. Facial dermatitis in children was also noted following the use of moist wipes containing the chemical. It was concluded that the continued use of the chemical in baby wipes and facial wipes will lead to increased rates of allergy to these preservatives in adults. The present study also noted three cases of contact allergy as occupational exposure from hand cleansers containing the chemical (Boyapati et al., 2013). Based on the results of a series of patch test conducted from 2011-2013, the Medical Journal of Australia reported a significant increase in the incidence of contact dermatitis in adult patients from the use of the baby wipes which contain the chemical (Cahill et al., 2014). In this report, the authors highlighted this remarkable rise of contact dermatitis from 3.5% in 2011 to 11.3% in 2013 among their patient population. The authors also noted that the chemical is now the most common cause of allergic contact dermatitis in their patient population (Cahill et al., 2014).

The Scientific Committee on Consumer Safety (SCCS) presented its opinion on the safety of the chemical (methylisothiazolinone) in consumer products. The committee concluded that, on the basis of current clinical data, the use of the chemical at 100 ppm in cosmetic products is not safe for the consumer. The committee also concluded that, for leave-on cosmetic products (including wet wipes), safe concentrations of the chemical for induction of contact allergy or elicitation have not been adequately demonstrated. Although a concentration of 15 ppm (0.0015%) of the chemical was considered safe for the consumer with respect to induction of contact allergy for rinse-off cosmetic products, no information was available for these products with respect to elicitation of contact allergy (SCCS, 2013).

**Repeated Dose Toxicity**

**Oral**

Based on the available data, the chemical is not considered to cause serious damage to health from repeated oral exposure.

No treatment related effects were observed in rats (Crl:CD BR strain) exposed to the chemical (up to 1000 ppm, equivalent to 65.7 and 93.5 mg/kg bw/day in males and females, respectively) in drinking water for three months. Dogs fed with diets prepared with the chemical for three months had a NOAEL of 1500 ppm (41 mg/kg bw/day) (CIR, 2010; US EPA, 1998).

Reasons for scheduling delegate’s interim decision and invitation for further comment

1 October 2015

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**Dermal**

No data were available for the chemical. Based on the available toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of toxicity, the chemical is not considered to cause serious damage to health from repeated exposure.

A formulation containing analogue chemical (2.55:1 ratio) was applied once daily for 91 days to the intact skin of Sprague Dawley (SD) rats by semi-occlusive dressing at doses of 0, 0.75, 3.75, or 18.75 mg/kg bw/day. Treatment-related skin reactions at all doses included slight to moderate erythema and desquamation, slight oedema and atonia, and eschar formation. Microscopic findings revealed treatment-related lesions such as inflammation, parakeratosis, and acanthosis at the treated sites. The LOAEL and NOAEL identified for local effects in this study, were = 0.104 and < 0.104 mg/kg bw/day (SCCS, 2009).

**Inhalation**

No data were available for the chemical. Based on the available inhalation toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of inhalation toxicity, the chemical is not considered to cause serious damage to health from repeated exposure through this route.

In a study conducted in accordance with OECD TG 413, Charles River Crl: CD(SD) BR rats were exposed to an aerosol product containing 14% of the analogue chemical for 13 weeks (0, 0.34, 1.15, or 2.64 mg/m³, at 6 hours/day, 5 days/week). At the top dose, effects included decreased bodyweight gain and signs consistent with sensory irritation such as chromorhinorrhea, rhinorrhea, eye squint, bradypnoea, and dyspnoea. Slight to moderate eosinophilic droplets in the anterior mucosa of the nasal turbinates and slight rhinitis in the lining of the nasal cavity were also reported at the top dose. At the mid-dose, slight incidence of rhinitis was observed. The study authors noted that eosinophilic droplets in the nasal turbinates and rhinitis were possibly reversible responses to upper respiratory tract inflammation. The lowest-observed-adverse-effect-concentration (LOAEC) and no-observed-adverse-effect-concentration (NOAEC) for this study were 2.64 and 1.15 mg/m³, respectively (SCCS, 2009; US EPA, 1998).

**Genotoxicity**

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies the chemical is not considered to be genotoxic.

The chemical was not mutagenic in Ames tests in *Salmonella typhimurium*, with or without metabolic activation (CIR, 2010; SCCNFP, 2003). The chemical (0.5-40 µg/mL) was also negative in an in vitro chromosome aberration study using the Chinese hamster ovary (CHO) cells, both with and without metabolic activation. In another study using CHO cells, chromosomal aberrations (at 3.75 µg/mL without S-9 activation (28 % aberrant cells) and at 7.50 µg/mL with S-9 activation (34 % aberrant cells) were seen accompanied by significant cytotoxicity (29-48 % reductions).
The chemical was reported to be negative in an in vivo mouse micronucleus assay (CIR, 2010; SCCNFP, 2003).

**Carcinogenicity**

No data are available for the chemical. Based on the weight of evidence from the available carcinogenicity study for the analogue chemical—3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone (CAS No. 55965-84-9), in which there was no evidence of carcinogenicity, the chemical is not likely to be a carcinogen.

In a two-year drinking water study on rats (CRL:CD BR) exposed to the analogue chemical, no treatment related neoplasms were observed up to the highest dose tested, 300 ppm (equivalent to 17.2 mg/kg bw/day). Hyperplasia of the forestomach was seen at mid and top doses. This was attributed to the corrosive nature of the chemical (CIR, 2010).

**Reproductive and Developmental Toxicity**

The chemical does not show specific reproductive or developmental toxicity.

In a two-generation reprotoxicity study, no treatment related effects were noted in rats (Crl:CD IGS BR strain) exposed to the chemical (up to 86 mg/kg bw/day in males and 115 mg/kg bw/day in females) through drinking water (CIR, 2010; US EPA, 1998).

Two teratogenicity studies showed no treatment related effect in rats (Crl:CD(SD) IGS BR strain) and rabbits (New Zealand White) exposed to the chemical at concentrations up to 40 and 30 mg/kg bw/day respectively. Based on the results, the maternal NOAELs were 20 (rats) and 10 (rabbits) mg/kg bw/day and developmental NOAELs were 40 (rats) and 30 (rabbits) mg/kg bw/day (CIR, 2010; US EPA, 1998).

**Neurotoxicity**

An acute in vitro neurotoxicity study of the chemical using cultures of embryonic rat (SD) cortical neurons and glia observed widespread neuroronal cell death within 24 hours in the cortical cultures exposed to 100 and 300 µM (highest concentration tested) concentrations. Gliotoxicity was low. Another 14-hour in vitro neurotoxicity study of the chemical concluded that prolonged exposures to the chemical and related isothiazolones may damage developing nervous systems (based on cell death observed in cultures treated with 3 µM concentration of the chemical along with changes in signalling complexes normally found in developing neurons) (CIR, 2010). However, no evidence of neurotoxicity was observed in vivo in the repeat dose or reproductive and developmental animal studies.

**Scheduling status**

Methylisothiazolinone is not specifically scheduled.

**Scheduling history**

Methylisothiazolinone has been previously considered for scheduling. In July 2014, the Advisory Committee on Chemicals Scheduling (ACCS), considered toxicological data on...
methylisothiazolinone and noted that its toxicological profile met the Schedule 6 factors of the Scheduling Policy Framework (SPF). The chemical is not a carcinogen or genotoxic. Based on the toxicity profile of this chemical, the committee considered that a Schedule 6 entry was warranted. The committee noted the maximum use concentration levels in both leave-on and rinse-off products (0.01%) overseas. In cleaning preparations the concentration level is typically reported to be <1% of methylisothiazolinone. The committee proposed, however, that a low concentration exemption cut-off to exclude methylisothiazolinone from the schedules is not warranted.

The committee was concerned about the reports that indicate an increased number of incidents of clinical sensitisation to methylisothiazolinone. They also noted a pre-meeting public submission that proposed deferral of the scheduling decision for cosmetic and domestic products intended for skin contact until the finalisation of the US Cosmetic Ingredients Review (CIR) report has been finalised and which was expected to be published later that year.

The committee recommended that a new Schedule 6 entry be created for methylisothiazolinone and that the delegate seek further information on non-cosmetic uses and possible exemptions. The committee agreed that the name methylisothiazolinone should be used in the Poisons Standard.

The delegate noted the committee’s recommendation and public submissions. He noted that the sensitising potential is the key driver for any scheduling action and the SPF criteria suggest this would warrant inclusion in Schedule 6 with and appropriate exemption for cosmetic and other products containing a low concentration of methylisothiazolinone. Therefore, the delegate decided to defer further consideration of scheduling methylisothiazolinone pending the publication of the final US CIR decision (CIR 2014).

*Pre-meeting public submissions*

Five public submissions were received. Most submissions pointed to the current international standards in place and one referred to a recent medical publication on acute dermatitis incidents related to MIT. The international standards referred to those in the USA, where MIT use is permitted at 100ppm or less for rinse-off products and in leave-on products when formulated to be non-sensitising, and in the EU, where MIT is still permitted at 100ppm but is officially reported to only to be safe in rinse-off products at 15ppm or less. One submission also pointed to adverse events data to one of their sunscreen products where no events were recorded for over a million items sold. Two submissions respectively requested that non-human use products, those not intended for skin use, such as paints, should be exempt from scheduling if containing levels 1000ppm or 100ppm or less.

All industry submissions requested a timeframe of 24 months to reformulate if scheduling was to progress for MIT.

The submission that comprised of a medical publication presented data of increasing incidences of acute dermatitis reactions to MIT, along with a public health warning by the SA Department of Health for products including MIT as a result of this medical publication, and warned of specific products such as baby wipes.

Summary of ACCS-ACMS advice to the delegate

The committee recommended a new Schedule 6 entry be created for methylisothiazolinone with appropriate exempt cut-offs.

The committee recommended an implementation date of 1 October 2017.

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

The reasons for the recommendations comprised the following:

- Preservative with increasing prevalence for skin sensitisation
- Preservative for use in cosmetics, therapeutic goods, industrial and household products
- Meets the criteria for Schedule 6; strong skin sensitiser

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;
- Other relevant information.

Delegates’ interim decision

The key issue driving the need to regulate methylisothiazolinone (MIT) by scheduling is its sensitisation potential. Following initial consideration by the ACCS in July 2014, and the publication of US Cosmetic Ingredients Review (CIR) and EU Scientific Committee on Consumer Safety (SCCS) reviews, the delegates have accepted advice from the joint meeting of the ACCS/ACMS to list methylisothiazolinone in Schedule 6, with exemptions for some types of cosmetics and therapeutic goods containing low concentrations. The delegates noted the increasing prevalence of reported skin sensitisation reactions and determined that the exemption cut-off of 0.0015% proposed by the EU SCCS could be protective for rinse-off cosmetics and therapeutic goods, but not for products applied to the skin and not intended to be washed off. The delegates determined that cosmetic and therapeutic goods intended for application to the skin without washing off posed an unacceptable sensitisation risk and should be included in Schedule 6. The delegates also determined that when methylisothiazolinone is present in products not intended for direct application to the skin, a higher exemption cut-off (0.1%) could be made in the Schedule 6 entry. The delegates noted that the proposed schedule changes could result in product sponsors needing to re-label, or possibly deciding to re-formulate products using other preservatives, and determined that a reasonably long period be allowed for such actions prior to
implementation of the scheduling decision. The delegates noted that the proposed EU restrictions could already be driving such changes. The delegates noted that some agricultural fungicides, insecticides and external use parasiticides could be affected by the scheduling change, but that most such products would fit within the 0.1% exemption.

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* to be: (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;

**Schedule entry**

**Schedule 6 – New Entry**

METHYLISOTHIAZOLINONE *except*:

a) in rinse off cosmetic preparations or therapeutic goods intended for topical rinse off application containing 0.0015 per cent or less of methylisothiazolinone; or

b) other preparations that are not for human use containing 0.1 per cent or less of methylisothiazolinone.

**Appendix F – New Entry**

<table>
<thead>
<tr>
<th>Poison</th>
<th>Warning statements</th>
<th>Safety direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHYLISOTHIAZOLINONE</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

The implementation date for this decision is 1 October 2017.

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

2.2 METHYLCHLOROISOTHIAZOLINONE (MCI)

**Scheduling proposal**

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

- to create a scheduling entry to prevent the use of methylchloroisothiazolinone when used in rinse-off cosmetics/personal care products or domestic products at concentrations above 0.0015, and
- *to create a schedule entry parallel to the restrictions for methylisothiazolinone for leave-on cosmetic/personal care products.*
Delegates’ reasons for referring this to the committee

The delegate asked the committee the following questions:

- The ACCS/ACMS is asked to advise on whether to adopt either the US CIR or EU SCCS sensitisation thresholds as an exemption cut-off from a new Schedule 6 entry for methylchloroisothiazolinone. Is there sufficient evidence that MCI may be a more potent sensitizer than MIT, and therefore require lower cut-offs? Given the difficulty of discriminating between the sensitisation potential of MCI when used alone, rather than in a MI/MCI combination, should the cut-offs for MCI mirror those recommended for MI?
- Alternatively, does the ACCS/ACMS support NICNAS advice that Schedule 6 controls are insufficient to protect the public and that consideration be given to listing in Appendix C (Schedule 10) with appropriate exemption cut-offs?
- Does the ACCS/ACMS advise that any schedule listing for methylchloroisothiazolinone be specific for cosmetic products, as outlined in the NICNAS report? Should different thresholds be proposed for products that are not intended to be directly applied to skin (e.g. cleaning products, deodorisers, antimicrobial gels and sprays)?
- Noting that methylchloroisothiazolinone is used at comparable concentrations in some therapeutic goods, but notably in sunscreen products that are directly applied to the skin, does the ACCS/ACMS advise that a schedule entry should specifically exempt such therapeutic goods or should they be subjected to the same exemption cut-offs as cosmetics?
- What weight should be given to the apparent lack of adverse reaction reports associated with the use of MCI in therapeutic goods (Attachment Y)?
- What regulatory impact might be expected in relation to registered AgVet products, given APVMA advice that the maximum concentration of MCI is of the order of 0.1-0.2% (Attachment X)?

Substance summary

Toxicokinetics

Toxicokinetic studies in rats using the chemical (CAS No. 26172-55-4) and its analogue (CAS No. 55965-84-9) show that it is readily absorbed and metabolised. The major metabolic products of the chemical are N-methylmalonamic acid (NMMA) and the 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propionamide. These studies did not report accumulation of the chemical or its metabolites in tissues. The chemical is widely distributed to all tissues in the body, with the highest level in the liver and lowest in the bone. It is eliminated within 24 hours mainly through urine, followed by bile and, finally, faeces.
An in vitro human skin absorption study conducted in accordance with OECD Test Guideline (TG) 428 reported maximum potential systemic bioavailability of the chemical as 84.5 % of the applied dose (NICNASa; SCCS, 2009).

**Acute Toxicity**

**Oral**

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia).

The analogue (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, MCI/MI—CAS No. 55965-84-9) had high acute toxicity in animal tests using oral exposure. Two studies where rats were administered the analogue chemical at 14 % reported the median lethal dose (LD50) at 64 mg/kg bw (69 mg/kg bw for male and 59 mg/kg bw for female rats). Observed sub-lethal effects included gastric irritation, lethargy and ataxia (CIR, 1992; SCCNFP, 2009).

**Dermal**

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia).

The analogue chemical (MCI/MIT, CAS No. 55965-84-9) had high acute toxicity in animal tests using dermal exposure. A study administered in rats using the analogue chemical as 14 % reported the LD50 at 141 mg/kg bw for both sexes. A similar study (administered as a 1.5 % formulation) in rabbits reported the LD50 as 113 mg/kg bw (CIR, 1992; SCCNFP, 2009).

**Inhalation**

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Very toxic by inhalation’ (T; R26) in HSIS (Safe Work Australia).

The analogue chemical (MCI/MIT, CAS No. 55965-84-9) exhibited high acute toxicity in animal tests using inhalation exposure. The median lethal concentration (LC50) in rats after a four-hour aerosol exposure was reported as 0.17 mg/L (IUCLID, 2000). Another study in rats reported the LC50 as 0.33 mg/L after a four-hour aerosol exposure. The major signs of toxicity were marked dyspnoea, salivation and death, and the principal lesions included pulmonary congestion, oedema, and haemorrhages (CIR, 1992; SCCS, 2009).

**Corrosion / Irritation**

**Skin Irritation**

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Causes burns’ (R34) in HSIS (Safe Work Australia).

The analogue chemical (MCI/MIT, CAS No. 55965-84-9) was found to be corrosive to rabbit skin when applied as a single semi-occluded application (at concentrations of 1.5 % and 14 %) to
shaved intact skin of New Zealand White rabbits in several studies (CIR, 1992; IUCLID, 2000). No other details were specified.

**Eye Irritation**

The chemical is recommended for classification as corrosive. It is expected that the undiluted chemical would be severely damaging to the eyes.

The analogue chemical (MCI/MIT, CAS No. 55965-84-9) was found to be corrosive to rabbit eyes in numerous Draize eye irritation studies using concentrations ranging from 1.1 % to 14 % (560–56,000 ppm). An aqueous dilution of 0.0056 % (56 ppm) was found non-irritating when tested in rabbit eyes for a period of four weeks (five days per week) (CIR, 1992).

The analogue chemical (CAS No. 55965-84-9) (undiluted) was also found to be an irritant in a bovine cornea study that measured opacity and permeability (CIR, 2010).

**Sensitisation**

**Skin Sensitisation**

The chemical is considered to be a skin sensitiser based on the positive results seen in several animal (guinea pig maximisation tests, Buehler test and local lymph node assays) and human studies.

In an in vitro assay, the chemical (MCI, CAS No. 26172-55-4) was found to be highly reactive towards glutathione, histidine and lysine and formed stable adducts (CIR, 2010).

A modified Buehler guinea pig maximisation test using Dunkin-Hartley guinea pigs found the chemical (MCI) to be a strong sensitiser at 0.1 %. A re-challenge with the chemical found that 50 % of the animals reacted to a lower concentration of 0.02 % (CIR, 2010).

A local lymph node assay (LLNA) study showed that the chemical (MCI) induced a strong lymph node cell proliferation in mice which correlated with protein binding and a guinea pig sensitisation assay (Potter and Hazelton, 1994). The PC200value (the concentration that produces a two-fold increase in mouse lymph node cell proliferation over controls) was 11 µg. The concentrations required to induce (IC50) and elicit (EC50) a response in 50 % of guinea pigs was 774 and 38 µg, respectively.

In an LLNA study with the analogue chemical (MCI/MIT, CAS No. 55965-84-9), EC3 values (an estimated concentration that will induce a stimulation index of 3 following topical application of the chemical) of 0.0082 (in acetone and olive oil vehicle) and 0.063 (propylene glycol vehicle) were determined. The chemical was characterised as a strong sensitiser. The data obtained correlated with cytokine profiling indicative of a skin sensitiser (NICNASa).

**Observation in humans**

The chemical has been reported to be an sensitiser in both cosmetic and occupational settings (NICNASa).
Data from multiple research centres conducted between 2010 and 2013 in Europe illustrates a rise in the frequency of sensitisation to the chemical from 4.4 to 8.3 %. Further, other pan-European data conducted between 2006 and 2008 illustrates a high prevalence of sensitisation (approximately 2—2.5 %) in eczema patients (SCCS, 2013).

In a study, 22 patients who were positive for sensitisation to the analogue (MCI/MI) were patch tested with the chemical at 300 ppm and all reacted positively. A follow up study showed that of 12 patients previously sensitised to MCI/MIT, all tested positive for the MCI/MIT at 150 ppm (SCCS, 2013).

Results from several patch tests indicate that the chemical has a strong potential to cause skin sensitisation and which correlated with the Open Epicutaneous Test (OET) (SCCS, 2013; NICNASa).

Further, patients sensitised to MIT also react to MCI while the opposite is not necessarily true (SCCS, 2013).

**Repeated Dose Toxicity**

**Oral**

Based on the available data, the chemical is not considered to cause serious health damage from repeated oral exposure.

No treatment-related effects were observed in rats (Charles River CD) exposed for three months to MCI/MIT (up to 800 ppm, equivalent to 29 mg/kg bw/day) in their diet.

In a drinking water study, no signs of adverse effects to any tissues or organs distant from the site of dosing were observed in rats (COBS SD) exposed to up to 225 ppm (20.5 mg/kg bw/day) of MCI/MIT for three months.

Dogs fed with diets prepared with MCI/MIT for three months showed no signs of systemic toxicity up to the highest tested dose levels of 30 mg/kg bw/day (SCCS, 2013).

**Dermal**

No data were available for the chemical. Based on the available toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of dermal toxicity, the chemical is not considered to cause serious damage to health from repeated exposure through this route (NICNASa).

**Inhalation**

No data were available for the chemical. Based on the available inhalation toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of inhalation toxicity, the chemical is not considered to cause serious damage to health from repeated exposure through this route (NICNASa).
**Genotoxicity**

Based on the weight of evidence from available in vitro and in vivo genotoxicity studies the chemical is not considered to be genotoxic (CIR, 1992; NICNASa; SCCS, 2009).

The genotoxic potential of the chemical was evaluated in several Ames (reverse mutation) tests with *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100. The chemical was mutagenic in the strain TA100 only without metabolic activation. MCI/MIT (CAS No. 55965-84-9) was mutagenic to strain TA100 and *Escherichia coli* in the Ames test. MCI/MIT also resulted in an increase in the mutant frequency in two gene mutation tests (mouse lymphoma cell line) both in the absence and presence of metabolic activation. An in vitro unscheduled DNA synthesis (UDS) assay using primary rat hepatocytes treated with MCI/MIT was negative. MCI/MIT showed no clastogenic activity when evaluated in an in vitro chromosome aberration test using Chinese hamster lung cells.

MCI/MIT in vitro studies yielded positive results that in vivo tests did not confirm. MCI/MIT showed negative results in micronucleus tests (mouse), chromosome aberration tests (mouse and rats), sex-linked recessive lethal tests in *Drosophila Melanogaster* and in two UDS studies in the rat.

Based on results from negative in vivo mutagenicity studies, along with negative carcinogenicity study for the analogue, the chemical is not considered to be genotoxic.

**Carcinogenicity**

No data are available for the chemical. The weight of evidence from the available carcinogenicity study for the analogue chemical—3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone (MCI/MIT, CAS No. 55965-84-9)—indicates there was no evidence of carcinogenicity. As this analogue contains the chemical at high concentrations, it also is not likely to be a carcinogen (NICNASa).

**Reproductive and Developmental Toxicity**

No data are available for this chemical. The weight of evidence from the available studies for the analogue chemical (MCI/MIT, CAS No. 55965-84-9) indicates that the chemical is not a specific reproductive or developmental toxin. As this analogue contains the chemical at high concentrations, it also is not likely to be a reproductive or developmental toxin.

In a two-generation reproductive toxicity study, no treatment-related effects were noted in rats (Crl:CD BR strain) exposed to MCI/MIT in drinking water (up to 300 ppm). A no observed adverse effect level (NOAEL) of 30 ppm was determined based on gastric irritation of the stomach at higher doses. The no observed effect level (NOEL) for reproductive toxicity was 300 ppm (the highest dose tested). There were no effects on fertility or foetal developmental parameters at any dose tested (SCCS, 2009).

Several teratogenicity studies showed no treatment-related effects in rats and rabbits exposed to MCI/MIT. Pregnant rabbits administered with MCI/MIT by gavage up to doses of 13.3 mg/kg bw/day, showed maternal toxicity at all doses. No visceral or skeletal malformations were found.
in the foetuses at any dose level. Pregnant Sprague Dawley (SD) rats exposed to MCI/MIT by
gavage (up to 15 mg/kg bw/day) showed maternal toxicity at all dose levels. Based on the
absence of any treatment-related effects on surviving dams and foetuses, a developmental NOEL
of 15 mg/kg bw/day was determined (CIR, 1992; SCCS, 2009).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation. The chemical may also
cause systemic acute toxicity (by all route of exposure) and local effects (skin corrosion and
possibly serious eye damage).

Public Risk Characterisation

The available information indicates that the chemical is widely used in Australia as a preservative
in cosmetic, personal care (including baby products), cleaning and laundry products. The
chemical is reported to be used in cosmetic/domestic products overseas at concentrations up to
0.1 % (HHDB).

Considering the range of domestic and cosmetic and personal care products that could contain the
chemical, the main route of public exposure is expected to be through the skin and inhalation
from products applied as aerosols.

In the absence of any regulatory controls, the characterised critical health effect (skin
sensitisation) has the potential to pose an unreasonable risk to the public through the identified
uses.

The risks could be mitigated by implementing concentration limits and restricting uses to rinse-
off products.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical
may occur, particularly where manual or open processes are used. These may include transfer and
blending activities, quality control analysis, and cleaning and maintaining of equipment. Worker
exposure to the chemical at lower concentrations can also occur while using formulated products
containing the chemical. The level and route of exposure will vary depending on the method of
application and work practices employed.

Given the critical systemic long-term, acute and local health effects, the chemical could pose an
unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and
inhalation exposure to the chemical are implemented. The chemical should be appropriately
classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a
workplace (such as an employer), has adequate information to determine appropriate controls.
**International regulations**

The use of MCI/MIT (CAS No. 55965-84-9), a 3:1 mixture of methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) is currently regulated in the EU with a maximum authorised mixture concentration of 0.0015 % (SCCS, 2009).

MCI/MIT is currently permitted at levels =0.0015 % (15 µg/mL or 15 ppm) in rinse-off products and =0.00075 % (7.5 µg/mL or 7.5 ppm) in leave-on products (Health Canada, 2011).

The Expert Panel of the Cosmetic Ingredient Review (CIR) recommended a concentration of 15 ppm MCI/MIT (76.7 % MCI and 23.3 % MI) for cosmetic rinse-off products and =7.5 ppm in cosmetic leave-on products (CIR, 1992).

The following exposure standards are identified (Galleria Chemica):

- An exposure limit—TWA of 0.2 mg/m³ and STEL of 0.4 mg/m³ was identified in Switzerland.

**Scheduling status**

Methylchloroisothiazolinone is not specifically scheduled.

**Scheduling history**

Methylchloroisothiazolinone has not been previously considered for scheduling.

Methylisothiazolinone, another similar chemical, is being re-considered for scheduling. In July 2014, the ACCS, considered toxicological data on methylisothiazolinone and noted that its toxicological profile met the Schedule 6 factors of the Scheduling Policy Framework (SPF). The chemical is not a carcinogen or genotoxic. Based on the toxicity profile of this chemical, the committee considered that a Schedule 6 entry was warranted. The delegate noted the committee’s recommendation and public submissions and noted that the sensitising potential is the key driver for any scheduling action. The delegate decided to defer further consideration of scheduling methylisothiazolinone pending the publication of the final US CIR decision.

**Pre-meeting public submissions**

Four public submissions were received. Most submissions pointed to the current international standards in place for MCI/MIT mix, such as it is permitted at 15ppm or less for rinse-off products or 7.5ppm or less for leave-on products. MCI/MIT mx was requested to be exempt from scheduling in industry products such as paints, adhesives, sealants, at 15ppm or less; this is what is currently in use.

One submission also pointed to adverse events data to one of their sunscreen products where no events were recorded for over a million items sold. Two submissions respectively requested that non-human use products, those not intended for skin use, such as paints, should be exempt from scheduling if containing levels 1000ppm or 100ppm or less.
All industry submissions requested a timeframe of 24 months to reformulate if scheduling was to progress for MIT.


**Summary of ACCS-ACMS advice to the delegate**

The committee recommended that a new Schedule 6 entry be created for methylchloroisothiazolinone with appropriate exempt cut-offs.

The committee recommended an implementation date of 1 October 2017.

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

The reasons for the recommendations comprised the following:

- Preservative with increasing prevalence for skin sensitisation
- Preservative for use in cosmetics, therapeutic goods, industrial and household products
- Meets the criteria for Schedule 6; strong skin sensitiser

**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;
- Other relevant information.

**Delegates’ interim decision**

As with methylisothiazolinone (MIT), the key issue driving the need to regulate methylchloroisothiazolinone (MCI) by scheduling is its sensitisation potential. The two substances were considered together by the ACCS/ACMS and this interim decision should be read in conjunction with that for MIT. The delegates accepted the advice from the ACCS/ACMS that MCI should be listed in Schedule 6, with exemption cut-offs comparable to MIT. The delegates also noted that MCI is not used as a preservative by itself, but usually in combination with MIT. Accordingly, the delegates determined that the cut-offs applied to MCI should refer to the combined concentrations.
The delegates noted that the industry request for a cut-off of 7.5ppm (0.00075%) for leave-on products is not necessary, because of the general exemption (0.001%) provided in Part 1 2(j) of the Poisons Standard.

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* to be: (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.

**Schedule entry**

**Schedule 6 – New Entry**

METHYLCHLOROISOTHIAZOLINONE except:

a) in rinse off cosmetic preparations or therapeutic goods intended for topical rinse off application containing 0.0015 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total; or

b) other preparations that are not for human use containing 0.0015 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total.

**Appendix F – New Entry**

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The implementation date for this decision is 1 October 2017.

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