Interim decisions & reasons for decisions by delegate of the Secretary to the Department of Health and invitation to provide further comments

November 2014

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 the 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 of the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect of the decision.

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 (published on 29 May 2014 at http://www.tga.gov.au/consultation-invitation/consultation-invitation-public-comment-accs-acms-and-joint-accsacms-meetings-july-2014). Edited versions of these submissions are available at http://www.tga.gov.au/public-submissions-scheduling-matters.

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 28 November 2014.

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, 2010), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at http://www.tga.gov.au/publication/ncctg-scheduling-policy-framework.

Persons making submissions are strongly encouraged to lodge submissions in electronic format (word or unsecured PDF preferred) via the email address provided below. Submissions, preferably in electronic format, should be made to:

The Secretary
Chemicals Scheduling Secretariat (MDP88)
Office of Chemical Safety
Department of Health

GPO Box 9848
CANBERRA ACT 2601
or by email to Chemicals.Scheduling@health.gov.au.

The closing date for further submissions is **28 November 2014**.

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:
http://www.health.gov.au/internet/main/publishing.nsf/Content/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.

Glossary

Abbreviation	Name
ACCC	Australian Competition and Consumer Commission
ACCS	Advisory Committee on Chemicals Scheduling
ACMS	Advisory Committee on Medicines Scheduling
APVMA	Australian Pesticides and Veterinary Medicines Authority
CAS	Chemical Abstract Service
CIR	Cosmetic Ingredient Review
CPS	Committee on Poisons Schedules
DPSSC	Drugs and Poisons Scheduling Sub-Committee
EPA	Environmental Protection Authority (United States)
FDA	Food and Drug Administration (United States)
IMAP	Inventory Multi-tiered Assessment and Prioritisation
ISO	International Standards Organization
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MOE	Margins Of Exposure
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee

Abbreviation	Name
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
OCS	Office of Chemical Safety
PAR	Prescription animal remedy
PEC	Priority existing chemical
PI	Product Information
PSC	Poisons Schedule (Standing) Committee
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SPF	National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [http://www.tga.gov.au/publication/ncctg-scheduling-policy-framework]
TGA	Therapeutic Goods Administration
TVL	Threshold Limit Value
WHO	World Health Organization
WS	Warning statement

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

1. Scheduling proposals referred to the July 2014 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#11)

1.1 FOSTHIAZATE

Scheduling proposal

The ACCS considered the following proposal referred by the chemicals scheduling delegate (the delegate) for advice:

- To include fosthiazate in either Schedule 6 or 7.

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

On 6 May 2014, the Office of Chemicals Safety (OCS), based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to register a new active ingredient, requested that the delegate consider including fosthiazate in Schedule 7 with no exemptions or cut-offs.

The reasons for this request are:

- Fosthiazate has a moderate oral toxicity in rats [LD_{50} 73 and 57 mg/kg bw (male and female respectively), with deaths];
- It has low to moderate dermal toxicity in rats [LD_{50} 2396 and 861 mg/kg bw (male and female respectively), with deaths];
- The inhalational toxicity is moderate [LC_{50} 832 and 558 mg/m^3 (rats male and female respectively), with deaths];
- It showed moderate eye irritancy potential in rabbits;
- It is a skin sensitiser in guinea pigs;
- Neurological effects (including tremor in rats treated dermally and orally, and uncoordinated movements and salivation in dogs treated orally) were observed at high dose levels in standard repeat-dose studies. Moreover, fosthiazate exhibited cholinesterase inhibition at low doses; and
- In a two-generation rat study clear evidence of offspring susceptibility was observed [reduced viability and weight gain in offspring at 30 ppm, and termination of the top dose group of 100 ppm (7.2/9.3 mg/kg bw/d) in males and females, respectively], after the first generation. In a rabbit developmental study a treatment-related decrease in the foetal body weight and increased frequency of small foetuses were noted at dose levels where no maternal toxicity was observed.

The delegate's reason for referring this scheduling proposal to the ACCS was that the OCS evaluation report noted that fosthiazate is a potential neurotoxicant and this warrants listing the

substance in Schedule 7. The *Scheduling Policy Framework for Medicines and Poisons*[1] (SPF) suggests that such submissions need consideration by the ACCS.

The delegate asked the ACCS the following specific question:

- The acute and repeat-dose toxicity profiles of fosthiazate are consistent with the *Scheduling Policy Framework for Medicines and Poisons* (SPF, 2010) factors for listing in Schedule 6. The basis for the Schedule 7 recommendation appears to be the very low NOAELs for cholinesterase inhibition (plasma, erythrocyte and brain) and LD_{50}s only slightly above the cut-off between Schedule 6 and Schedule 7, particularly in females. Does the ACCS support listing in Schedule 7?

- Note that a scheduling cut-off is not yet proposed because no product containing fosthiazate has been submitted for registration. At the time of referral by the delegate, no comment had been received from the sponsor on the OCS scheduling recommendation.

Substance summary

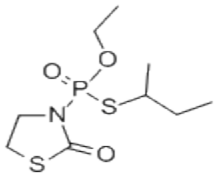

Figure 1. Structure of fosthiazate

Fosthiazate is a relatively new group non-fumigant, organophosphorus (OP) nematicide. It also has systemic activity against various species of insects and mites on the foliar parts of the plants. Fosthiazate has been on the market in Japan since 1993 and is currently registered for use on potatoes for controlling cyst nematodes in the U.K[2].

Organophosphorus pesticides are used extensively to control agricultural, household and structural pests. These pesticides constitute a diverse group of chemical structures exhibiting a wide range of physicochemical properties, with their primary toxicological action arising from inhibition of the enzyme acetylcholinesterase (AChE)[2]. Pope (1999)[3] considered whether OP pesticides all exert toxicity through a common mechanism and evaluated the comparative toxicity of the 38 OP AChE inhibitors registered for use as pesticides in the United States. It is concluded that all OP anticholinesterases potentially have a common mechanism of toxicity, that is, phosphorylation of AChE causing accumulation of acetylcholine, overstimulation of cholinergic receptors, and consequent clinical signs of cholinergic toxicity. Additional macromolecular targets for some OP pesticides, however, may alter the cascade of events following AChE phosphorylation and thereby modify that common mechanism. Furthermore, other macromolecular targets of some OP pesticides appear capable of altering noncholinergic neurochemical processes. These additional actions may contribute to qualitative and quantitative differences in toxicity sometimes noted in the presence of similar levels of AChE inhibition induced by different OP pesticides. Further investigation of these additional sites of action may allow subclassification and influence the decision to perform combined risk assessments on this class of pesticides based on common mechanism of toxicity.

[1] National Coordinating Committee on Therapeutic Goods (NCCTG): *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2010) [http://www.tga.gov.au/publication/ncctg-scheduling-policy-framework]
[2] Santanu Mukherjee, Surendra Kumar, Anjana Srivastava and Prakash Chandra Srivastava (2011). Uptake and distribution of 14C-labeled Fosthiazate in tomato (*Lycopersicon esculentum* L.) Agricultural Sciences, Volume 2, No.3, p 308-312.
[3] Pope C. N (1999) Organophosphorus pesticides: do they all have the same mechanism of toxicity? Journal of Toxicology and Environmental Health, Part B Critical Review, 1999 April-June; 2(2):161-181.

Acute toxicity

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

TOXICITY	*SPECIES*	*FOSTHIAZATE*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	73 and 57 (M/F), with deaths	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	2396 and 861 (M/F), with deaths	Low to moderate to high toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	832 and 558 (M/F), with deaths	Moderate to high toxicity
Skin irritation	Rabbit	Non irritant	
Eye irritation	Rabbit	Moderate irritant	
Skin sensitisation (Magnussen & Kligman method)	Guinea pig	Sensitiser	

Repeat-dose toxicity

Short-term and sub-chronic studies in rats, mice and dogs reported cholinesterase inhibition in plasma, erythrocytes and the brain as the main effect at low doses with no observed effect levels (NOEL) of 0.05–0.1 mg/kg bw/d by the oral route across species. Target organs identified at higher doses than those which caused cholinesterase inhibition were the liver and adrenals, with a range of organ weight and histopathological changes observed.

A short-term repeat dose dermal study in rats elicited similar responses to those seen in the oral studies, with cholinesterase inhibition (plasma, erythrocyte) at low doses (2.5 mg/kg bw/d in females) and inhibition in all three regions (plasma, brain and erythrocyte) at ≥25 mg/kg bw/d in both sexes. Histopathological and weight changes were observed in the adrenals at higher doses.

Long term studies in rats, mice and dogs were consistent with the shorter duration repeat dose studies.

Genotoxicity

Fosthiazate was negative in *in vitro* and *in vivo* in genotoxicity studies.

Carcinogenicity

There was no evidence of carcinogenic potential in rats or mice in long-term studies.

Reproduction and developmental toxicity

In a two-generation rat study, there was an increase in irregular oestrous cycles, slightly reduced conception rate and fertility index, and a tendency towards prolonged gestation lengths in females. However overall, most of these identified effects were within historical control ranges, and no evidence of reproductive toxicity was observed (noting that sperm parameters and sexual maturation data were not collected). Offspring viability post-partum and weight gain in the first

offspring generation were affected by treatment at the mid (30 ppm) and highest dose tested (100 ppm), with subsequent termination of the reproductive study for the highest dose level only in the second generation. No evidence of treatment-related macroscopic, histopathological or developmental changes was observed in F_1 or F_2 offspring.

Fosthiazate was not a developmental toxicant in rats; however, in rabbits there was an increase in small foetus frequency and a slight reduction in body weights in foetuses at 2 mg/kg bw/d, which was the dose established as the maternal NOEL (being the highest dose tested in the study). However, fosthiazate is not a teratogen, as no treatment-related visceral or skeletal malformations or variations were seen at all doses tested in developmental toxicity studies. Therefore, on the weight of evidence from evaluated data, it is unlikely that fosthiazate is a developmental toxicant.

Observation in humans

No information was provided.

Public exposure

The evaluation report indicated that as no product has been proposed for registration, exposure estimation was not required at this time.

International regulations

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

In the EU, fosthiazate was included in the Annex I of the Directive in September 2003 (Commission directive 2003/84/EC) with the following: "Specific provisions: Only uses as nematicide may be authorised". The EU has been reviewing this regulation, but the Secretariat has been unable to access the latest EU regulation for the substance.

In the US, the US Environmental Protection Authority notes that 'available data provide adequate information to support the conditional registration of fosthiazate technical and end-use products for use on tomatoes'.

In Taiwan, 75% emulsifiable concentrate (EC) fosthiazate is banned (effective 1 January 2014)[4].

Scheduling status

Fosthiazate is not specifically scheduled.

Several organophosphates are included in Schedules 6, including acephate and vamidothion, and Schedule 7, including amiton and terbufos. Tolclofos-methyl is listed in Schedule 5.

Scheduling history

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

Pre-meeting public submissions

No public submissions were received.

[4] Available at [https://agrochem.chemlinked.com/news/agrochemical-news/taiwan-bans-fosthiazate-75-ec-and-restricts-other-3-formulated-pesticides].

Summary of ACCS advice to the delegate

The ACCS recommended that a new Schedule 7 entry be created for fosthiazate with an implementation date of 1 February 2015.

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

The reason for the recommendation is:

- Chronic toxicity profile is consistent with Schedule 7 factors.

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[5];
- Other relevant information.

Delegate's interim decision

The delegate accepts the advice tendered by the ACCS and agrees to include a new entry for fosthiazate in Schedule 7. The toxicity profile of fosthiazate is consistent with that of other neurotoxicant organophosphonates and potentially with the SPF criteria for listing in Schedule 6. However, effects on offspring and some uncertainties about the chronic toxicity profile (quite low NOEL for inhibition of brain cholinesterase in repeated exposure studies), as well as reports of some lethality via eye exposure, all support a more conservative listing in Schedule 7.

Schedule entry

SCHEDULE 7 – New entry

FOSTHIAZATE.

The implementation date for this decision is 1 February 2015.

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

1.2 METOFLUTHRIN

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To amend the current Schedule 6 metofluthrin entry to exclude mosquito repellent preparations containing 312 g/kg or less of metofluthrin from scheduling.

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

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

On 4 April 2014, the APVMA, based on an application to amend the current metofuthrin entry, requested that the delegate consider a proposal to amend the current Schedule 6 listing of metofluthrin to exempt mosquito repellent preparations containing 312 g/kg or less of metofluthrin from scheduling.

The delegate's reason for referring this scheduling proposal to the ACCS was that as a re-scheduling application the SPF suggests that such submissions need consideration by the ACCS. The specific product under consideration is a battery-driven device that releases metofluthrin from an impregnated fabric pad into the atmosphere around the product user.

The delegate asked the ACCS the following specific questions:

- The original OCS evaluation report and advice from the February 2011 ACCS meeting noted in particular the inhalation toxicity profile in support of the recommendation to list metofluthin in Schedule 6, with no exemption. In the absence of any new submitted data on the specific insect repellent product, the OCS's view is that the toxicity/hazard profile of the product is considered to be comparable to that of the active. Does the ACCS consider that a sufficient case has been made by the applicant to consider re-scheduling the specific insect repellent product? If so, does the ACCS support its exemption from Schedule 6, or listing in Schedule 5?

- The ACCS may wish to take into consideration the sponsor's arguments and an expert report sought by the APVMA relating to the issue of the MOE estimates for adults and children, as they relate to the proposed label warning statements and safety directions (particularly those relating to avoidance of inhalation), but the ACCS is reminded that such label statements are no longer within the jurisdiction of the scheduling delegate.

Substance summary

Metofluthrin is a pyrethroid ester. It evaporates readily and therefore requires no external heat[6]. Majority of pyrethroids are derived by modifying the chrysanthemic acid moiety of pyrethrin I and esterifying the alcohols. Synthetic pyrethroids have been developed to improve the specificity and activity of pyrethrins, while maintaining the high knockdown and low terrestrial vertebrate toxicity. Pyrethrins, pyrethroids, DDT and DDT analogues belong to a group of chemicals that are neurotoxic and share a similar mode of action that is distinctive from other classes of insecticides.

Pyrethroids have been classified toxicologically into two subclasses based on the induction of either whole body tremors (T-syndrome) or a coarse whole body tremor progressing to sinuous writhing (choreoathetosis) with salivation (CS-syndrome) following near-lethal dose levels in both rats and mice, and closely follows the chemical structure of the two types of pyrethroids. Type I pyrethroids are characterized by the T-syndrome which consists of aggressive sparring, sensitivity to external stimuli, fine tremors progressing to whole body tremors and prostration. Type I pyrethroids also elevate core body temperature, which is attributed to the excessive muscular activity associated with tremors. Type II pyrethroids are characterized by the CS-syndrome which is comprised initially of pawing and burrowing behaviour followed by profuse salivation, choreoathetosis and increased startle.

Increasing the dose levels of pyrethrins and pyrethroids results in a proportional increase in motor activity, which is the classic dose-response effect with respect to neurotoxic substances. Pyrethrins and pyrethroids act very quickly to produce symptoms of lost coordination and paralysis, which are

[6] Metofluthrin Pesticide Fact Sheet. United States Environmental Protection Agency. Available at [http://www.epa.gov/opp00001/chem_search/reg_actions/registration/fs_PC-109709_01-Sep-06.pdf].

known as 'the knockdown effect', and which are often accompanied by spasms and tremors that induce intense repetitive activation in sense organs and in myelinated nerve fibers. The spasms can be violent and can cause the loss of extremities, such as legs and wings in insects [7].

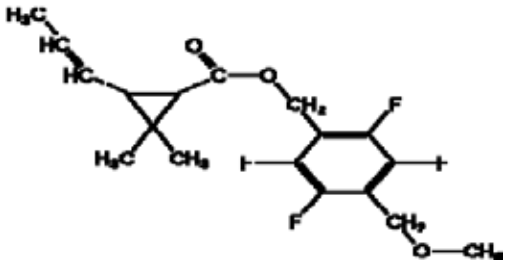

Figure 2. Structure of metofluthrin

Acute toxicity

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

TOXICITY	*SPECIES*	*METOFLUTHRIN*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	>2000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rats	>1080 and ≤1960 mg/m^3 (one death at 1080 mg/m^3, all animals died at 1960 mg/m^3)	Moderate to high toxicity
Skin irritation	Rabbits	slight	
Eye irritation	Rabbits	Not an eye irritant	
Skin sensitisation (guinea pig maximisation test)	Guinea pig	Negative	

Repeat-dose toxicity

In a four-week repeat-dose inhalation toxicity study, 10 rats/sex/dose were exposed (nose-only) to the mist aerosol of metofluthrin at doses of 0, 9.84, 50.6, 98.7 or 196 mg/m^3 for 4 hours/day for 28 days (OCS indicated that the duration of exposure recommended by OECD 412 is for 6 hours/day). Seven males and three females died at 196 mg/m³. Gross necropsy was performed on all animals that died, the cause of death, however, could not be absolutely determined. Clinical signs seen immediately following exposure at 196 mg/m^3 were tremor, hypersensitivity, ataxic gait, tiptoe gait,

[7] Jerome J. Schleier and Robert K. D. Peterson (2011) Pyrethrins and Pyrethroid Insecticides. Chapter 3 RSC Green Chemistry No. 11 Green Trends in Insect Control. Edited by Oscar Lopez and Jose G. Fernfmdez-Bolafios Published by the Royal Society of Chemistry. [www.rsc.org]. Available at [http://www.afpmb.org/sites/default/files/pubs/dwfp/publications/FY11/Schleier_Peterson_2011.pdf].

clonic convulsion, hypothermia and lateral position which were observed in males until day 26 and in females until day 24 of exposure. There was an increased incidence of tail tremor and tremor at 196 mg/m^3 (days 1-4) in both sexes. There was a significant but transient reduction in food and water consumption in males at 196 mg/m^3 on day 3 of exposure. These changes may be related to neurologic signs as they were only noted at the beginning of exposure. There were no treatment-related changes in bodyweight, urinalysis, ophthalmology, haematology or blood biochemistry. The no observed effect level (NOEL) was 98.7 mg/m^3 based on increased mortality, clinical signs and atrophy of the pancreas and submandibular gland in males and females at 196 mg/m^3.

In a one-month oral toxicity study 12 rats/sex/dose were administered with metofluthrin in the diet at concentrations of 0, 300, 1000 or 3000 ppm. An additional 6 rats/sex/group were administered metofluthrin in the diet at concentrations of 0 or 3000 ppm for one month, followed by a two-week recovery period. One female was found dead on day 4 of treatment at 3000 ppm. Prior to death, tremor was observed in this animal and gross pathology showed dark changes and enlargement of the liver. Tremor was observed during days 2-5 in males and females at 3000 ppm, but disappeared by day 11 in males and day 7 in females. These changes may be related to the appearance of neurologic symptoms in the early phase of treatment. There was a significant increase in the absolute liver weight in males and females at 3000 ppm, and relative liver weight at 1000 and 3000 ppm. Liver effects observed during gross pathology and histopathology included dark changes in the liver of females at 1000 ppm and in both sexes at 3000 ppm, hepatocellular hypertrophy in both sexes at 1000 and 3000 ppm, a decrease of slight or mild diffuse hepatocyte vacuolation in both sexes at 3000 ppm, and an increased amount of smooth endoplasmic reticulum in two males at 3000 ppm. These changes were not observed at the end of the recovery period. The NOEL was 300 ppm (equivalent to 28.6 mg/kg bw/d) in males, based on reduced bodyweight, bodyweight gain, increased cholesterol and phospholipid levels, and histopathological changes to the liver in males at 1000 ppm.

Mutagenicity

Metofluthrin was not mutagenic in a bacterial reverse mutation assay with and without metabolic activation.

Genotoxicity

It was not genotoxic in an *in vitro* chromosomal aberration assay in Chinese hamster lung cells with and without S9. Additionally, no evidence of a genotoxic potential was seen in an *in vivo* micronucleus test in the mouse.

Neurotoxicity

In an acute neurotoxicity study, a single dose was administered via gavage to groups of 10 male and 10 female rats, at doses of 0, 20, 50 or 100 mg/kg bw. At 100 mg/kg bw, two male rats and one female rat were found dead shortly after treatment, and four female rats were sacrificed due to their moribund condition. Adverse clinical signs noted in these rats prior to death or sacrifice included clonic convulsions, tonic extensor convulsions, continuous whole body tremors, intermittent whole body twitches, tachypnoea, prostration, lost righting reflex, soft or liquid faces and hyperpnoea.

Carcinogenicity

In two studies, rats were administered metofluthrin at doses of 0, 200, 900, 1800 or 3600 ppm via the diet, daily for seven days. In each study a positive control group was administered sodium phenobarbital (NaPB) at 1000 ppm via the diet daily for seven days. Overall, rats treated with metofluthrin exhibited affected enzyme induction at 900 ppm and above. Liver morphology was observed at 1800 ppm and above, as evidenced by increased liver weight, hepatocellular hypertrophy, hepatocyte cell DNA synthesis and CYP2B expression. In addition, a decrease in

hepatocytic vacuolation and hepatic gap junction intracellular communication (GJIC) was observed. All of these effects diminished upon cessation of treatment. Generally, rats treated with NaPB at 1000 ppm displayed similar effects on the liver to those treated with metofluthrin. The mode of action for tumour induction in rats may be similar to that of NaPB. NaPB induces rodent liver tumours by a non-genotoxic mechanism characterised by increased cell proliferation, hypertrophy and the development of altered hepatic foci. Furthermore, NaPB is known to cause an increase in the activity of CYP P450 enzymes CYP2B1 and CYP2B2 *in vivo*. Enzyme induction of CYP2B in particular, due to the activation of nuclear receptors such as the constitutive androstane receptor (CAR), has been correlated with liver tumour formation in rodents and is accompanied by an increase in CYP mRNA and protein synthesis. NaPB is a barbiturate that has been widely used in humans as a sedative, hypnotic and anti-epileptic, and for which no increased incidence of liver tumours has been observed.

The effect of metofluthrin and NaPB on the induction of CYP2B forms (50 μM for each) and replicative DNA synthesis (10-1000 μM for each) was evaluated in cultured rat and human hepatocytes. Treatment of cultured rat and human hepatocytes with metofluthrin or NaPB induced expression of CYP2B, with NaPB producing a greater response than metofluthrin. These results are similar to the above *in vivo* studies where metofluthrin induced microsomal CYP2B in rat liver. In contrast to the above effects of metofluthrin and NaPB, a marked species difference was observed in the effects on replicative DNA synthesis (i.e. cell proliferation). Both metofluthrin and NaPB induced replicative DNA synthesis in rat but not human hepatocytes suggesting that one of the key events in the proposed MOA for metofluthrin (and NaPB) induced rat liver tumour formation (increased cell proliferation) does not occur in human hepatocytes *in vitro*.

The human relevance of the rat liver carcinogenic response was then discussed in relation to the human relevance framework. Treatment with high doses of metofluthrin (900 and 1800 ppm) for two years produced an increased incidence of hepatocellular adenomas and/or carcinomas in rats. Treatment with metofluthrin induced cytochrome P450 (CYP) CYP2B isoform (increased smooth endoplasmic reticulum), resulting in increased liver weights which were associated with centrilobular hepatocyte hypertrophy and induction of increased hepatocellular DNA replication. These key events in the metofluthrin induction of liver tumours were observed at or below tumourigenic dose levels. Induction of CYP2B by metofluthrin was shown to involve activation of CAR in rat hepatocytes. This MOA is similar to that of NaPB, which is known to be non-genotoxic, a CAR activator and inducer of liver CYP2B isoforms. In rodents, NaPB exhibits a clear threshold for the induction of hepatocellular tumours, and the available data indicates that metofluthrin is less potent than NaPB in its induction of rodent liver tumours. Furthermore, extensive epidemiological data for NaPB (a widely used anticonvulsant with a long history of use) indicates that it is not a human carcinogen. Limited studies in human hepatocytes *in vitro* suggest that NaPB does not increase hepatocellular proliferation indicating that the key event of NaPB induced liver tumour in rats (i.e. increased cell proliferation) does not occur in the human liver. Consequently, by analogy metofluthrin is not expected to produce an increase in hepatocellular proliferation in humans and therefore, would not result in liver tumour formation. Liver effects in rats occurred only after treatment at high doses of metofluthrin and human exposure to such dose levels is not expected. Therefore, metofluthrin is not expected to pose a carcinogenic risk to humans.

Reproduction and developmental toxicity

In a two-generation reproduction study, groups of rats (12/sex/dose) were fed diets containing 0, 50, 200, 1000 or 1800 ppm of metofluthrin for 70 days before pairing, throughout pairing, gestation and lactation and until termination. One F1 control male was found moribund and sacrificed during the post-weaning period. During lactation, there was an increase in the number of P-generation females with tremor and twitches at 1800 ppm, and F1 females with tremor, twitches and excessive salivation at 1000 and 1800 ppm. There were no treatment-related clinical signs of toxicity observed in F1 pups, however, tremor was observed in F2 pups on postpartum day 24 at 1800 ppm,

and this was considered to result from pups eating the test substance. Among the P-generation, there was a transient reduction in female bodyweight gain at all dose levels during pre-cohabitation. Throughout lactation, bodyweight was reduced at 1000 and 1800 ppm and bodyweight gain was reduced at 1800 ppm and there was also a reduction in absolute and relative food consumption at 1800 ppm. There were no treatment-related changes in bodyweight, bodyweight gain or food consumption during gestation. In F1-generation animals, throughout the post-weaning period, there was a reduction in bodyweight for males at 1800 ppm and females at 1000 and 1800 ppm. Bodyweight gain was also reduced during the first two weeks of the post-weaning period at 1800 ppm in males and at all dose levels in females. In F1 females, bodyweight gain was also reduced at 1800 ppm throughout post-weaning. Bodyweight was reduced in F1 females throughout gestation and lactation at doses of 1000 and 1800 ppm and bodyweight gain was reduced in early gestation. Food consumption was reduced in F1 females at 1000 and 1800 ppm during post-weaning period, gestation and lactation.

Observation in humans

No information was provided.

Public exposure

The product is intended only for domestic use as a personal mosquito repellent and not be used directly on food or food preparation areas or food utensils. Exposure to the product will be *via* the inhalational and dermal routes, with the potential for incidental oral exposure in children from touching (hand to mouth transfer) or mouthing the device or refills. Exposure can occur when using the product or when replacing the refill unit in the device.

The product is intended to be used on a person or next to a person during outdoor activities throughout the year. The public may be exposed to the product while replacing the refill unit. There is a potential risk to users and bystanders associated with repeat exposure to the product.

A total margin of exposure (MOE) derived by adding dermal and inhalation MOE values) of more than 100 was obtained in adults, 2 to less than 3 years old and 1 to less than 2 years old children (229, 654 and 546, respectively). A MOE of 100 or above is considered acceptable. The MOE takes into account both interspecies extrapolation and intra-species variability.

International regulations

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

In the EU, metofluthrin is included in Annex I of the Directive 98/8/EC. Biocidal products containing active substances that have been included in Annex I or IA of the Biocides Directive are subject to product authorisation or registration, respectively, as per the requirements of the Biocides Directive.

In New York state (USA) two products, OFF! Insect Repellent Fan and OFF! Insect Repellent Fan Refill, containing metofluthrin have been registered with the following condition: ‘The registrant is required to provide us with a summary of any adverse effects that have been associated with these products, including any FIFRA 6(a)(2) reports, on a quarterly basis’.

In Canada, a product of OFF! Clip-on Mosquito Repellent (Pest Control Product Registration Number 30211) was registered for use as a personal insect repellent in October 2011. Within the first year of its registration, the Pest Management Regulatory Agency (PMRA) received six human incident reports associated with this product. A wide range of symptoms such as dizziness, swelling, nausea, lethargy, muscular weakness, pruritus, irregular heart rate, or loss of consciousness was noted. The effects reported were considered to be either possibly or probably related to pesticide exposure. The product currently holds a registration that is conditional upon the

submission of additional data on product exposure. The PMRA indicated that 'Although only a few incidents were reported, this is a new product and the PMRA will continue to monitor incidents reported in the following year'.

Scheduling status

Metafluthrin is listed in Schedule 6.

Other synthetic pyrethroids, namely transfluthrin (in Schedule 6), permethrin (in Schedules 4, 5 and 6), deltamethrin (in Schedules 5, 6 and 7), esfenvalerate (in Schedules 5 and 6) and alpha-cypermethrin (in Schedules 5, 6 and 7) are included in various schedules of the SUSMP.

Scheduling history

In 2011, the chemicals scheduling delegate, based on the advice from the ACCS, decided to include metofluthrin in Schedule 6.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The ACCS recommended that the current Schedule 6 metofluthrin entry be amended to exempt impregnated fabric mosquito repellent preparations for use in a vaporizer containing 15 mg or less of metofluthrin per disk to Schedule 5.

The ACCS recommended an implementation date of 1 February 2015.

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

The reason for the recommendation is:

- The packaging and presentation of the product mitigates the exposure risk and warrants Schedule 5 inclusion.

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 accepts the advice tendered by the ACCS and agrees to include a new entry for metofluthrin in Schedule 5 and to amend the current Schedule 6 entry. While metofluthrin is a moderately toxic pyrethroid insecticide, the packaging and presentation of the product mitigates the exposure risk and warrants Schedule 5 inclusion.

Schedule entry

SCHEDULE 6 - AMENDMENT

METOFLUTHRIN except when included in Schedule 5.

SCHEDULE 5 – NEW ENTRY

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

The implementation date for this decision is 1 February 2015.

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

1.3 2-HYDROXYPROPYL METHACRYLATE

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To create a new Schedule 5 entry for 2-hydroxypropyl methacrylate with appropriate concentration cut-offs for preparations containing low concentrations of 2-hydroxypropyl methacrylate.

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

On 23 April 2014, the National Industrial Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment Prioritisation (IMAP) programme, requested that the delegate consider a proposal to include 2-hydroxypropyl methacrylate in Schedule 5. The reasons for the recommendation are that the substance is a skin sensitiser and may also cause skin and eye irritation.

The delegate's reason for referring this scheduling proposal to the ACCS was that the NICNAS IMAP report noted 2-hydroxypropyl methacrylate's sensitisation potential and recommended inclusion in Schedule 5, with a low level cut-off to exempt from scheduling and appropriate warning statements to avoid skin contact. While this particular cosmetic ingredients is not currently listed in the schedules, there are entries for related esters, methyl and ethyl methacrylates. ACCS advice is needed to determine the most appropriate schedule and to advise on potential regulatory impacts.

The delegate asked the ACCS the following questions:

- Does the ACCS support the NICNAS recommendation to list 2-hydroxypropyl methacrylate in Schedule 5, with Appendix F warning statements to avoid skin contact?
- Are there sufficient similarities between the toxicological profiles of the methyl, ethyl and 2-hydroxypropyl esters of methacrylate to use current schedule entries as a template? Methyl methacrylate is currently listed in Schedule 6, with exemptions for preparations containing 1% or less, and for cosmetic use (but note that cosmetic uses of methyl methacrylate are proscribed via listing in Appendix C). Ethyl methacrylate is listed in Schedule 5, but only for cosmetic use and is exempt from scheduling in preparations containing 1% or less. To what extent are these entries consistent with the NICNAS recommendation?

- Note that the Minutes of the February 2007 meeting of the NDPSC include a detailed discussion of the rationale for setting a 1% exemption for both methyl and ethyl methacrylates. Is such an exemption cut-off appropriate for 2-hydroxypropyl methacrylate?

- Is listing under the name 2-hydroxypropyl methacrylate appropriate, given that it is usually a mixture of two isomers with different CAS numbers - 2-propenoic acid, 2-methyl-, monoester with 1,2-propanediol (CAS No. 27813-02-1) and 2-propenoic acid, 2-methyl, 2-hydroxypropyl ester (CAS No. 923-26-2)?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *2-hydroxypropyl methacrylate*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=855.

The NICNAS scheduling proposal is based on the assessment of two substances: 2-propenoic acid, 2-methyl-, monoester with 1,2-propanediol (CAS No. 27813-02-1) and 2-propenoic acid, 2-methyl, 2-hydroxypropyl ester (CAS No. 923-26-2). NICNAS indicated that 2-propenoic acid, 2-methyl-, monoester with 1,2-propanediol (CAS No. 27813-02-1) consists of two isomers. This occurs due to the method of industrial production, which is usually either the reaction between methacrylic acid and propylene oxide, or methacrylic acid esterification of 1,2-propanediol. The predominant isomer is the secondary alcohol 2-propenoic acid, 2-methyl, 2-hydroxypropyl ester, which is assigned the CAS No. 923-26-2. Therefore toxicity information for both CAS No. 923-26-2 and CAS No. 27813-02-1 is considered to be applicable to both chemicals. NICNAS indicated that their evaluation report is a human health Tier II assessment for 2-hydroxypropyl methacrylate and their scheduling recommendation is for structurally related methacrylates.

Scheduling status

2-Hydroxypropyl methacrylate is not specifically scheduled. Other methacrylates, namely methyl methacrylate (MMC) and ethyl methacrylate (EMC) are listed in the SUSMP. Methyl methacrylate is listed in Schedule 6, Appendices C and F. Ethyl methacrylate is listed in Schedule 5 and Appendix F.

SCHEDULE 6

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

(a) for cosmetic use; or

(b) in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

APPENDIX C

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

APPENDIX F

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

SCHEDULE 5

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

APPENDIX F

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

Scheduling history

In May 1974, the Drugs and Poisons Scheduling Sub-Committee (DPSSC) decided to include EMC along with several dozen other compounds in Appendix B without any clear rationale being recorded.

In August 1995, the NDPSC decided to delete the entire Appendix B entry. The NDPSC felt that Appendix B was being misinterpreted. It was also noted that jurisdictions did not in general adopt Appendix B.

In February 2003, the NDPSC agreed to reinstate Appendix B, including the EMC, listing.

In October 2006, the NDPSC considered MMC for the first time and also reconsidered EMC. The NDPSC decided to include cosmetic preparations containing EMC in Schedule 5 and Appendix F. The NDPSC also decided to delete the Appendix B entry for EMC. The NDPSC agreed that Schedule 6 (excluding derivatives) and Appendix F entries may be appropriate for MMC and decided to foreshadow this decision.

In February 2007, the NDPSC decided to include MMC in Schedule 6 and Appendices C and F.

Pre-meeting public submissions

One submission was received. The submission noted that the substance is not regulated in EU or the USA, therefore a schedule listing for the substance is not required. If, however, a warning statement "avoid contact with skin" is required, appropriate transition time should be allowed e.g. for amendments to labels, 12-24 months from the publication of the final decision would be required.

Summary of ACCS advice to the delegate

The ACCS recommended that nail preparations containing 2-hydroxypropyl methacrylate be listed in Schedule 5 except when labeled 'avoid contact with skin'.

The ACCS recommended an implementation date of 1 July 2015.

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

The reason for the recommendation is:

- Its current wide use in nail preparations where application may result in skin contact means management of the risk of skin sensitisation through labelling is required.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts ACCS advice that a new Schedule 5 entry be created for 2-hydroxypropyl methacrylate. Its toxicological profile is consistent with the SPF criteria for Schedule 5, including relatively low acute toxicity, skin/eye irritancy and sensitisation potential. The delegate notes, and accepts, ACCS advice that the entry be specific for its use in cosmetic products used on the cuticles (nails). The toxicity of 2-hydroxypropyl methacrylate appears to be less severe than the methyl- and ethyl-methacrylates currently listed in Schedule 5, 6 and Appendix C, although there is some potential for cross-sensitisation to occur between these methacrylate derivatives when used in nail preparations. The delegate accepts ACCS advice that a 'reverse scheduling' exemption from Schedule 5 could apply for products labelled with a warning statement '*avoid contact with skin*'. Since the Schedule 5 listing is specific for products used on the nails, there is no need for a similar warning statement in Appendix F, because application of such a warning statement via Appendix F would actually exempt any Schedule 5 product.

Schedule entry

SCHEDULE 5 – New entry

2-HYDROXYPROPYL METHACRYLATE in nail preparations **except** when labeled 'avoid contact with skin'.

A long implementation time is necessary to allow for orderly relabelling of any affected products, therefore **the implementation date for this decision is 1 July 2015.**

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

to be used and the extent of use of a substance; (c) the toxicity of a substance and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

1.4 3-ISOTHIAZOLONE, 2-METHYL- OR METHYLISOTHIAZOLONE

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To list 3-isothiazolone, 2-methyl- in an appropriate schedule with concentration cut-offs for low concentration preparations.

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

On 23 April 2014, NICNAS, under its IMAP programme, requested that the delegate consider a proposal to include cosmetic/personal care preparations containing 3-isothiazolone, 2-methyl- (referred here as methylisothiazolone) in an appropriate schedule with low concentration exemption cut-off to exempt from scheduling. The reasons for this request are that the substance is a skin sensitiser and may also cause systemic acute toxicity (by all routes of exposure) and local effects (skin corrosion and the possibility of causing serious damage to eyes).

The delegate's reason for referring this scheduling proposal to the ACCS was that the IMAP report highlights the sensitisation potential of methylisothiazolone in cosmetic and other products and noted that international controls over its use in cosmetics limits the concentration to 0.01%. NICNAS proposed inclusion in a schedule of the SUSMP, with a low-concentration cut-off to exempt from scheduling. The sensitisation potential was also highlighted in a recent report in the *Medical Journal of Australia* by Cahill *et al*, 2014, particularly in association with its use in 'wet wipes'.

The delegate asked the ACCS the following questions:

- Does the ACCS agree that the toxicity profile for methylisothiazolone (acute lethality, skin/eye irritancy and sensitisation potential) is consistent with listing in Schedule 6?
- Which name should be used for any schedule entry – methylisothiazolone, 2-methylisothiazol-3(2H)-one or 3-isothiazolone, 2-methyl-?
- Can the ACCS recommend a cut-off to a lower schedule, or exempt from scheduling for products containing a low concentration level of methylisothiazolone? Should this cut-off be 0.01%, as specified in several international regulations cited in the NICNAS IMAP report?
- What weight should be given to reports of allergic reactions in humans at concentrations in currently used 'wet wipes' and other products, as reported by Cahill *et al*, 2014? Despite evidence from animal and *in vitro* studies that suggest a higher concentration threshold for sensitisation reactions, are these clinical reports consistent with others in the NICNAS IMAP report (including an assessment by the European SCCS) that contact allergies can occur at concentrations much lower than 0.01%?
- What are the likely regulatory impacts on existing consumer products if the ACCS recommends listing in a schedule with no cut-off?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *3-isothiazolone, 2-methyl-*. This report is publicly available on the NICNAS website:

http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1062.

Scheduling status

Methylisothiazolone is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

Seven submissions were received.

The first submission requested that industrial and other preparations containing methylisothiazolone be excluded from scheduling. The submission also indicated that the consideration should be referred to the joint ACCS/ACMS meeting once the Cosmetic Ingredient Review (CIR) report is finalised.

The second submission requested the consideration should be deferred until final recommendations of the CIR report are available or if a decision is made which affects products currently on the market, the implementation date should be extended to 24 months.

The third submission indicated that aqueous dispersion preparations containing low concentrations of methylisothiazolone are considered not to be skin sensitisers. If a low concentration exemption cut-off of below 0.1% is chosen, this should be supported by toxicity and user data.

The fourth submission indicated that scheduling of methylisothiazolone may have impact on therapeutic preparations containing methylisothiazolone and suggested the substance should be consideration by the joint ACCS/ACMS. The submission did not object to harmonising cut offs.

The fifth submission supported regulatory alignment with overseas and harmonisation of appropriate risk management measures.

The sixth submission indicated that it did not believe in a “one size fits all applicability”, due to the variability in end products and uses. A subsequent submission states that products that do not have direct skin applications be exempted from scheduling due to lower risk profile. If cut-offs are applied to domestic preparations containing methylisothiazolone, they should be in line with those within Australia’s hazardous substances classification scheme.

The seventh submission requested any cut-off assigned to methylisothiazolone be for cosmetics only.

Summary of ACCS advice to the delegate

The ACCS recommended that the delegate foreshadow that a new Schedule 6 entry be created for methylisothiazolone and to seek further information on non-cosmetic uses and possible exemptions. This matter should be referred to a joint meeting.

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 was unable to make a scheduling recommendation relating to methylisothiazolone. The sensitising potential is the key driver for any scheduling action and the SPF criteria suggest this would warrant inclusion in Schedule 6, with an appropriate exemption for cosmetic and other products containing a low concentration. There is a significant disparity between the outcomes of the 2014 EU CSSR review of methylisothiazolone (no safe level of exposure in cosmetics) and the draft US CIR 2014 review (suggesting a cut-off at 100 ppm). The ACCS decided it would be prudent to await the final US CIR panel review before proceeding to set a cut-off for a foreshadowed Schedule 6 listing. The ACCS also noted that the matter should go to a joint meeting of the ACCS/ACMS, given the importance of this preservative in therapeutic goods as well as cosmetics.

The delegate's interim decision was therefore to defer further consideration of the scheduling of methylisothiazolone, pending the publication of the final US CIR decision. Further consideration of the scheduling of methylisothiazolone should involve referral to a joint meeting of the ACCS and ACMS, in order to consider potential impacts associated with its use in therapeutic goods, as well as scheduling consideration of the closely related preservative 5-chloro-2-methylisothiazolone. This is a position supported in most of the public submissions received.

1.5 DIETHYLENE GLYCOL MONOMETHYL ETHER OR ETHANOL, 2(2-METHOXYETHOXY)

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- Proposal to develop a separate listing for diethylene glycol monomethyl ether in Schedule 6 to complement the current generic listing of diethylene glycol monoalkyl ethers and to consider restrictions on use in cosmetic preparations.

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

On 29 August 2013, NICNAS, under its IMAP programme, recommended that the delegate consider creating a Schedule 6 entry for preparations containing diethylene glycol monomethyl ether for domestic use and a Schedule 7 entry for preparations containing diethylene glycol monomethyl ether for cosmetic use.

The basis for this recommendation was that developmental toxicity is the main concern and as cosmetic use potentially involves direct dermal application, a Schedule 7 entry for cosmetic products is applicable.

The delegate's reason for referring this scheduling proposal to the ACCS was that diethylene glycol monomethyl ether (DEGME) may be currently covered by the generic Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates. There is a 10% cut-off to exempt these from scheduling.

A related chemical (hexyloxyethanol) was referred to the July 2013 ACCS meeting, which recommended listing in Schedule 6 as a separate entry from the generic entry for ethylene glycol monoalkyl ethers.

The NICNAS IMAP report on DEGME included recommendations for strengthening hazard statements and concentration restrictions on use in products such as cosmetics, household cleaners, paints and floor sealants. The advice of the ACCS is needed to implement any scheduling amendments.

The delegate asked the ACCS the following questions:

- The NICNAS IMAP assessment particularly notes potential developmental toxicity with relatively high oral no observed adverse effect levels (NOAELs), although somewhat lower dermal NOAELs. The report also notes risk assessments suggesting a relatively low margin of exposure (MoE) for some uses of DEGME (particularly in cosmetics). Does the ACCS consider that Schedule 6 listing (with 10% cut-off to exempt from scheduling) remains appropriate for DEGME?
- Is there a need to include an entry in Appendix C to prohibit the use of DEGME in cosmetic (or other domestic products?) at concentrations above those listed in the NICNAS IMAP report?
- Are the current First Aid statements, Warning Statements and Safety Directions in Appendices E & F for scheduled products containing DEGME appropriate?
- Does the current entry for ethylene glycol monoalkyl ethers in Appendix I (Uniform Paint Standard) adequately address uses of DEGME?
- What information would be needed to assess the regulatory impacts of any proposed changes to the scheduling of DEGME (e.g. in AgVet products)?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *ethanol, 2-(2-methoxyethoxy)-* available at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=76.

Scheduling status

Ethanol, 2-(2-methoxyethoxy)- is not specifically scheduled. Ethylene glycol monoalkyl ethers and their acetates are listed in Schedule 6 and Appendices E, F and I.

Scheduling history

In November 1984, the Poisons Schedule (Standing) Committee (PSC) considered scheduling of ethylene glycol monoalkyl ethers and their acetates. The PSC noted that ethylene glycol monomethyl- and monoethyl ethers were the most toxic of the series which demonstrated significant testicular effects, reproductive toxicity, haematological effects and were toxic at inhalation levels at the TLV. The PSC also noted that other alkyl ethers of demonstrated haematological effects which increased with chain lengths. The PSC therefore decided to include preparations containing 5% or less ethylene glycol monoalkyl ethers and their acetates in Schedule 6.

In February 1985, the PSC reconsidered the November 1984 decision and decided to raise the Schedule 6 ethylene glycol monoalkyl ethers and their acetates exemption cut-off from 5% to 10%.

Pre-meeting public submissions

One submission was received. The submission indicated that the substance is not used in cosmetic products in Australia and it has no objection to aligning with EU regulations.

Summary of ACCS advice to the delegate

The ACCS recommended that preparations for cosmetic use containing diethylene glycol monomethyl ether be included in Appendix C.

The committee also recommended that a new Schedule 6 entry be created for diethylene glycol monomethyl ether and that the delegate seeks further information on non-cosmetic uses, possible exemptions and labelling.

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 the substance; (b) the purposes for which the substance is to be used and its extent of use; and (c) the toxicity of the substance;

The reasons for the recommendation comprised the following:

- The reproductive toxicity of the substance.
- The substance is readily absorbed through the skin.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate noted that diethylene glycol monomethyl ether (DEGME) is a diethylene glycol ether, and that it would not be covered by the generic Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates. The toxicological profile of DEGME includes potential developmental and reproductive toxicity and is therefore comparable to related substances covered by Schedule 6 entries. The delegate therefore proposes to accept ACCS advice that a separate listing for DEGME in Schedule 6 is warranted. The delegate also notes the low MOE estimates associated with its direct application to the skin in cosmetic products, and accepts ACCS advice that a separate listing be created in Appendix C for this use.

The delegate notes that the ACCS was unable to recommend an exemption cut-off for the proposed Schedule 6 entry. In accepting this scheduling proposal, the delegate invites further public comment on any perceived regulatory impacts of a Schedule 6 entry with no cut-off.

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

Schedule entry

SCHEDULE 6 – New entry

DIETHYLENE GLYCOL MONOMETHYL ETHER.

APPENDIX C - New entry

DIETHYLENE GLYCOL MONOMETHYL ETHER for cosmetic use.

The delegate has decided on an implementation date of 1 June 2015 for this scheduling decision. This is to enable further consultation on the implications of not proposing an exemption cut-off for the Schedule 6 entry.

1.6 LINEAR ALKYLBENZENE SULFONATES (C10-C16)

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To develop a generic entry for linear alkylbenzene sulfonates (C10-C16), with appropriate low concentration exemption cut-offs. This may also require an amendment to the current Schedule 5 and Appendices E and F entries for sodium dodecylbenzene sulfonate to reflect this generic entry. A further proposal is to include liquid laundry detergents in capsule preparations containing linear alkylbenzene sulfonates (C10-C16) in Schedule 6.

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

On 23 April 2014, NICNAS, under its IMAP programme, requested that the delegate consider a proposal to amend the current Schedule 5 sodium dodecylbenzene sulfonate (SDS) entry to include all other substances in the linear alkylbenzene sulfonate (LAS) group. NICNAS also requested that the delegate consider including liquid laundry detergent capsule preparations containing LAS in Schedule 6 with appropriate low concentration cut-off to exempt from scheduling.

The reasons for this request are:

- the critical health effects for risk characterisation include systemic acute effects (acute toxicity by the oral route of exposure) and local effects (eye damage and skin irritation);
- the substances in this group may also compromise the integrity of the skin and increase dermal absorption of other chemicals present in LAS containing product formulations;
- acute oral toxicity via damage to the mucous membranes has been reported in children exposed to high concentrations of chemicals in liquid laundry detergent capsules containing MEA dodecylbenzene sulfonate;
- where high concentrations may be used in domestic and cosmetic products, the potential risk of accidental contact with the eye is a concern. Incidental oral exposure resulting in oral toxicity is considered less likely given the types of products in which the chemicals are used, with the exception of liquid laundry detergent capsules;
- accidental exposure of the chemicals to children, by ingestion and eye and skin contact, has occurred from liquid laundry detergent capsules, which rapidly dissolve in contact with moisture. In some cases referral to a hospital was required (Australian Competition and Consumer Commission (ACCC)). The likelihood of exposure in these cases is much greater than that expected from bulk packaged laundry detergents. The packaging format and fixed volume also enables rapid exposure to a concentrated dose of the chemicals. The ACCC has

stated that the liquid laundry detergent capsules in their current form are highly attractive to children given the transparent packaging and bright colours. As there is some concern for children's safety, the ACCC and the relevant industry participants are working together to improve the safety and packaging of these products, should these chemicals be used in liquid laundry detergent capsules in their current form (Accord); and

- additionally, the chemicals in this group are frequently formulated with related chemicals with similar toxicity including alcohol ethoxylates, laureth sulfates and lauryl sulfates. The risk of cumulative toxicological effect is also a concern. This should be taken into account when considering the appropriate regulatory framework for these chemicals.

The delegate's reason for referring this scheduling proposal to the ACCS was that 18 surfactant compounds have been referred for consideration under the generic title LAS. The scheduling history of this group of compounds is complex. They were last considered by the National Drugs and Poisons Schedule Committee (NDPSC) in 1998. At that time, the NDPSC made a decision to include sodium dodecylbenzene sulfonate in Schedule 5, with a 30% cut-off to exempt from scheduling. It is clear that the NDPSC considered a generic listing for LAS, but refrained from doing so because of incomplete knowledge of the toxicological profiles of the full range of such surfactants and concerns about the regulatory impact on existing uses associated with either a Schedule 5 or Schedule 6 listing. There is an indication that a possible 20% exemption cut-off was considered to lessen the potential regulatory impact.

The delegate asked the ACCS the following questions:

- In the light of toxicological issues raised in the NICNAS IMAP report (acute toxicity, severe skin/eye irritancy), does the ACCS support the development of a generic entry for LAS in either Schedule 5 or Schedule 6? Should such a generic entry specify the chain length (C10 - 16)?

- Would a generic entry capture all of the salts identified in the NICNAS IMAP report, including those salts with ethanolamine? Is there any potential overlap with the current Schedule 5 entry for ethanolamine (that excludes its salts and derivatives)?

- Is there sufficient evidence to support a cut-off to exempt from scheduling at either 30% (the current cut-off for sodium dodecylbenzene sulfonate) or 20% (the cut-off considered by the NDPSC in 1998), or an even lower figure? Note that the above possible cut-offs are well above the likely threshold for eye irritancy (perhaps as low as 0.01 - 1%).

- Is there a need to create a separate listing in Schedule 6 for LAS in liquid laundry preparations, when packaged in soluble capsules, in order to address the specific child poisoning concerns raised in the NICNAS IMAP report?

- Is there a need to amend the current Schedule 5 entry for sodium dodecylbenzene sulfonate to align with any proposed generic LAS entry?

- Are the current First Aid, Warning Statements and Safety Directions for sodium dodecylbenzene sulfonate in Appendices E & F also suitable for a generic LAS entry?

- The 1998 NDPSC noted that there is potentially a wide range of LAS in use in Australian detergent products, as well as potential surfactant uses in existing AgVet products. Can the ACCS offer any advice on the regulatory impact of a recommendation to develop a generic schedule entry for LAS?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *linear alkylbenzene sulfonates (C10-C16)*. This report is publicly available on the NICNAS website:

http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=939.

Scheduling status

Linear alkylbenzene sulfonate is not listed in the Schedules. Sodium dodecylbenzene sulfonate has been specifically listed in Schedule 5 and Appendices E and F.

SCHEDULE 5

SODIUM DODECYLBENZENE SULFONATE **except** in preparations containing 30 per cent or less of sodium dodecylbenzene sulfonate.

APPENDIX E

Poisons	Standard statements
Sodium dodecylbenzene sulfonate	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). G3 - If swallowed, do NOT induce vomiting. E2 - If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

APPENDIX F

Poisons	Warning statements	Safety direction
Sodium dodecylbenzene sulfonate	79 Will irritate eyes.	1 Avoid contact with eyes.

Scheduling history

SDS was first considered at the May 1997 National Drugs and Poisons Schedule Meeting (NDPSC). The NDPSC considered potassium peroxomonosulfate and SDS and decided to include potassium peroxomonosulfate in Schedule 6 and indicated that, based on its toxicological profile, SDS should be included in Schedule 6. NDPSC, however, expressed concern that SDS may already be in widespread use and wished to give industries that may be affected an opportunity to comment on the scheduling. Therefore, the NDPSC decided to foreshadow the inclusion of SDS in Schedule 6.

In May 1998, the NDPSC considered the May 1997 foreshadowed decision and discussed whether it was appropriate to establish a group entry for LAS under Schedule 6, based on a lowest oral LD_{50} value for LAS of 404 mg/kg in rats, severe dermal irritancy of 15% aqueous solutions of SDS and LAS in rabbits, and severe ocular irritancy of SDS in rabbits. The NDPSC noted that the evaluator indicated that the Cosmetics Ingredient Review Expert Panel had concluded that SDS, triethanolamine dodecylbenzene sulfonate and sodium decylbenzene sulfonate "are safe as cosmetic ingredients in the current practices of use". The NDPSC also noted that although the International Programme on Chemical Safety review highlighted a need for further studies, there were no adverse

conclusions as to consumer safety. For these reasons, it was suggested that it may be possible to limit the scope of scheduling of these substances to their use in agricultural/veterinary products. Following discussion, the NDPSC agreed to classify SDS as a Schedule 5 substance instead of a Schedule 6 substance. Overall, the NDPSC supported a Schedule 5 classification for SDS, with exemption from scheduling being permitted for products containing 20% or less of SDS provided these products were labelled to warn of potential eye irritancy. The NDPSC also decided to include SDS in Appendices E and F.

In August 1998, the NDPSC, based on the public submissions presented in the requests for reconsideration, and particularly the advice that products containing up to 30% SDS are being marketed, agreed with the proposal that the cut-off from Schedule 5 to exempt should be raised to 30%. The NDPSC agreed also that, in view of the long history of use of domestic products containing SDS with little evidence of harm, warning statements should not be required on unscheduled products.

Pre-meeting public submissions

Two submissions were received. Both submissions requested that the current schedule listing of the substance is appropriate, i.e. no change required.

Summary of ACCS advice to the delegate

The ACCS recommended that LAS compounds have been used in the domestic laundry market for a very long time and the product safety and exposure is well characterised. The committee does not consider that additional scheduling controls are required.

However, safety concerns have arisen as a consequence of the relatively new presentation of liquid laundry capsules. The committee is aware of the steps already taken by the ACCC and industry to develop an industry Guideline for Labelling and Packaging of these products and recommended a review in 12 months to determine its impact and to reconsider whether scheduling of these substances is recommended.

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 the scheduling history of this group of substances and that the current advice from the ACCS is consistent with previous deliberations of the NDPSC. While the delegate agrees that the toxicological profile of this group of substances is consistent with SPF criteria for listing in Schedules 5 and 6, the long history of use in domestic washing and detergent products without apparent need for scheduling controls is a pertinent factor in the delegate's interim decision NOT to create a specific entry covering all the substances in this group, nor to amend current listings in Schedules 5 and 6 for related substances. The delegate notes the potentially significant regulatory

impact of broadening schedule entries for this group of substances and determines that such actions are not warranted on the basis of demonstrated or perceived risk, as opposed to the potential hazard based on their intrinsic toxicity. The delegate notes safety concerns associated with new detergent product types and the attempts to resolve these issues through consumer safety laws and application of an industry code. The delegate awaits the outcome of these initiatives before any further reconsideration of scheduling of this group of substances.

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

1.7 NICKEL, SOLUBLE SALTS

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To amend the current Schedule 6 nickel sulfate entry to read nickel, soluble salts.

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

On 24 April 2014, NICNAS, under its IMAP programme, requested that the delegate consider a proposal to amend the current Schedule 6 nickel sulfate entry to read 'nickel, soluble salts'. This is to include other similar nickel substances such as soluble nickel compounds, nickel chloride and nickel nitrate, and nickel fluoride in Schedule 6 due to their similar toxicological properties (i.e. carcinogenic, genotoxic and developmental toxicity potential.)

The delegate's reason for referring this scheduling proposal to the ACCS was that the NICNAS IMAP reports on soluble nickel salts raise a number of toxicological issues that warrant scheduling consideration and require advice from the ACCS. The key toxicology issues include acute toxicity, sensitisation, genotoxicity, and carcinogenicity. Nickel sulfate is already listed in Schedule 6, on the basis of actions of the former NDPSC in 1996 when it considered an ingredient of a swimming pool chemical product. The NICNAS IMAP report proposals represent a substantial broadening of the current entry, and may capture a range of products not currently scheduled.

The delegate asked the ACCS the following questions:

- Are there likely to be any consumer products available for retail sale that contain soluble nickel salts and that may require scheduling? Note the NICNAS IMAP report includes the following summary: '*Given the site-limited uses identified for the chemical, it is unlikely that the public will be exposed to chemicals of this group. Although, the public may come into contact with articles/coated surfaces containing the chemical, it is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Therefore the risk to the public is not considered to be unreasonable.'*

- In framing any scheduling recommendations, is it necessary to consider the REACH regulations addressing the potential for soluble nickel ions to be released from ear rings, ear piercings, necklaces etc?

- If the current nickel sulfate Schedule 6 entry is to be broadened, is there sufficient information to propose a cut-off to exempt nickel sulfate from scheduling where the health risks do not require control via scheduling?

- If a generic listing for NICKEL, SOLUBLE SALTS is adopted, is there sufficient definition of the term 'soluble' to enable the specific compounds to be identified?
- There are currently no entries in Appendices E or F for nickel sulfate. Are such entries needed if the Schedule 6 entry is broadened to include all soluble nickel salts?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment reports *for soluble nickel compounds (group 1)*, *nickel chloride*, and *nickel nitrate and nickel fluoride*. These reports are publicly available on the NICNAS website:

- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=839;
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=878; and
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=883.

Scheduling status

All concentrations and use patterns of nickel sulfate are currently included in Schedule 6.

SCHEDULE 6

NICKEL SULFATE.

Scheduling history

In February 1996, the NDPSC decided to list nickel sulfate in Schedule 6 in view of its acute oral toxicity and skin sensitisation potential.

Pre-meeting public submissions

One submission was received. The submission supported the delegate's proposal.

Summary of ACCS advice to the delegate

The ACCS recommended that soluble nickel compounds such as nickel chloride, and nickel nitrate and nickel fluoride do not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The NICNAS IMAP reports outline the quite significant toxicity potential for nickel and its compounds, including carcinogenicity and respiratory/skin sensitisation potential. The many industrial applications of nickel and its compounds attract stringent regulatory controls, including prohibition under carcinogenicity regulations. There is extensive evidence of sensitising potential associated with the use of nickel metal in jewellery, cutlery and clothing studs, resulting in enhanced regulatory restrictions (EU REACH regulations) on nickel leaching from these uses.

The current Schedule 6 entry for nickel sulfate was listed in 1996 to regulate its specific use in a swimming pool chemical. The delegate notes that neither the NICNAS IMAP report, nor the advice from the ACCS, identified a potential use for any other soluble nickel salts in products that would be available on the domestic retail market. This is a key reason behind the ACCS advice that the Schedule 6 entry for nickel sulfate does not need expansion to capture other soluble nickel salts. The ACCS also advised that it would be inappropriate to use the SUSMP to regulate the use of metallic nickel in jewellery, cutlery etc.

The NICNAS IMAP reports include the following statement about potential public exposures:

Given the site-limited uses identified for the chemical, it is unlikely that the public will be exposed to chemicals of this group. Although, the public may come into contact with articles/coated surfaces containing the chemical, it is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Therefore the risk to the public is not considered to be unreasonable.

Accordingly, the delegate's interim decision is to NOT expand the current Schedule 6 entry for nickel sulfate to include other soluble nickel salts, on the basis that there is no identified public health risk for products available on the retail market, other than the currently registered swimming pool chemical.

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; and (c) the toxicity of a substance.

1.8 N-METHYL-2-PYRROLIDONE

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To amend the N-methyl-2-pyrrolidone Schedule 5 and Schedule 6 entries.

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

On 23 April 2014, NICNAS, under its IMAP programme, requested that the delegate consider a proposal to amend the current Schedules 5 and 6 N-methyl-2-pyrrolidone (NMP) entries. NICNAS recommended that the concentration of the substance in cosmetics/personal care products and domestic products be restricted. The reason for this request is the toxicity profile at concentrations reported to be in use indicate that N-methyl-2-pyrrolidone be considered for listing in Schedule 6, consistent with the SPF guidelines.

The delegate's reason for referring this scheduling proposal to the ACCS was that the NICNAS IMAP report on N-methyl-2-pyrrolidone draws attention to the developmental toxicity potential of this solvent, and to international actions to limit its concentration in cosmetics and other domestic products. It is noted that its reproductive toxicity potential was considered by the NDPSC during the 1990s, at which time it was considered that the findings were 'inconclusive' and the NDPSC

decided to retain N-methyl-2-pyrrolidone in Schedule 6, with cut-offs to 50% for Schedule 5 listing and 25% for exempt, consistent with it also being listed as a *designated solvent*. There is also a listing in Schedule 5 for a veterinary product containing a high concentration of N-methyl-2-pyrrolidone, but where the pack volume was only 2 ml.

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the new information on the reproductive toxicity potential of N-methyl-2-pyrrolidone warrants re-consideration of its current scheduling? Does this imply that the stem listing in Schedule 6 remains appropriate, but that adjustments need to be made to the Schedule 5 and exempt cut-offs?
- Given the advice of the NICNAS IMAP report, reflecting its and international assessments of the safety of using N-methyl-2-pyrrolidone in cosmetic and other domestic products, how does the ACCS advise on using schedule listing to achieve an appropriate restriction on the concentration allowed in such products?
- What weight should be given to the proposed reclassification proposal under REACH legislation that would lower the specific concentration limit for classification as reproductive toxic category 1B from 5% to 0.3%? If adopted, this will effectively restrict the use of NMP in consumer applications to <0.3%. This would be an effective ban on such products because NMP would have no functionality at this level in present consumer applications.
- Should N-methyl-2-pyrrolidone be removed from the list of 'designated solvents' or should other adjustments be made to this listing? Does Part 2 Clause 7(k)(iv) need amending?
- There are currently First Aid statement requirements in Appendix E, but no entry in Appendix F. Is there a need to develop warning statements in Appendix F?
- What are the likely to be the regulatory impacts on other types of products (consumer, AgVet and therapeutic) that incorporate N-methyl-2-pyrrolidone as a solvent or ingredient?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment and Prioritisation (IMAP) human health Tier II assessment report for *2-pyrrolidinone, 1-methyl-*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=91.

Scheduling status

N-methyl-2-pyrrolidone is currently listed in Part 1, Interpretation and Schedule 5, Schedule 6, and Appendix E.

PART 1, INTERPRETATION

"Designated solvent" means the following:

N-methyl-2-pyrrolidone

SCHEDULE 5

N-METHYL-2-PYRROLIDONE:

(a) when packed in single use containers having a capacity of 2 mL or less; or

(b) in preparations containing 50 per cent or less of N-methyl-2-pyrrolidone or preparations containing 50 per cent or less of a mixture of any two or more of N-methyl-2-pyrrolidone, N-

(N-octyl)-2-pyrrolidone or N-(N-dodecyl)-2-pyrrolidone **except** in preparations containing 25 per cent or less of designated solvents.

SCHEDULE 6

N-METHYL-2-PYRROLIDONE **except**:

(a) when included in Schedule 5; or

(b) in preparations containing 25 per cent or less of designated solvents.

It is also included in Appendix E with the following statements.

APPENDIX E

When included in Schedule 5

Poisons	Standard statements
N-methyl-2-pyrrolidone	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). G3 - If swallowed, do NOT induce vomiting. E1 - If in eyes wash out immediately with water.

When included in Schedule 6

Poisons	Standard statements
N-methyl-2-pyrrolidone	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). G3 - If swallowed, do NOT induce vomiting. E2 - If in eyes, hold eyelids apart and flush the eyes continuously with water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.

Other similar substances namely, N-(n-dodecyl)-2-pyrrolidone and N-(n-octyl)-2-pyrrolidone are listed in Schedule 5.

Scheduling history

NMP was first listed in Schedules 5 and 6 in November 1997 by the NDPSC. The NDPSC supported the scheduling of NMP in Schedule 6, with a cut-off at 50% to Schedule 5. Exemption from scheduling at a low concentration had not been supported because there had been concerns relating to the teratogenicity of NMP in a rat study which had failed to determine a no effect level for NMP. The NDPSC also noted that literature contained a number of reports indicating that NMP did have reproductive toxicity potential and, therefore, it was difficult to support an exemption at any level for this substance.

In February 1998, the NDPSC agreed that NMP should be included in the list of 'designated solvents' and that a cut-off from Schedule 5 be established for preparations containing 25% or less of designated solvents. It was noted that there was some argument about the interpretation of teratogenicity results, and the committee considered the available data on the reproductive effects of NMP to be inconclusive.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The ACCS recommended that the current scheduling of N-methyl-2-pyrrolidone 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

The disparity of the advice available to the delegate relating to the potential reproductive and developmental toxicity of N-methyl-2-pyrrolidone makes the scheduling decision difficult. The difficulty for the delegate is compounded by the wide use of N-methyl-2-pyrrolidone across a range of product types and the consequent regulatory impact of any change to its scheduling. The delegate notes that the ACCS has effectively supported previous scheduling consideration by the NDPSC, concluding that the evidence of reproductive toxicity and developmental toxicity (in the presence of significant maternal toxicity) was inconclusive or lacked sufficient detail for an informed evaluation. On the other hand, the NICNAS report cited international regulatory actions under REACH that classifies N-methyl-2-pyrrolidone as 'reprotoxic category 1B' and limits its use in several product types, including in cosmetics. The difficulty for the delegate is further compounded by the fact that the NICNAS recommendations are based primarily on recent (2009 & 2010) OECD and EU reviews, in which some of the critical studies on developmental and reproductive toxicity are 'newer', while others had been available to the NDPSC in its 1997 and 1999 reviews. Noting that the reproductive and developmental toxicities reported in both older and more recent studies occurred at quite high dose rates (oral, dermal and inhalational) and in the presence of significant maternal toxicity, the delegate is inclined to accept the advice of the ACCS, that the current listings of N-methyl-2-pyrrolidone in Schedules 5 and 6 remain appropriate, along with the current entry in Appendix E.

Therefore, the delegate's interim decision is to make no changes to the current entries for N-methyl-2-pyrrolidone in Schedules 5 and 6.

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; and (c) the toxicity of a substance.

1.9 PHENOL, 2-AMINO OR O-AMINOPHENOL

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To add restrictions for domestic use and to include phenol, 2-amino in Appendix C for cosmetic use.

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

On 23 April 2014, NICNAS), under its IMAP programme, requested that the delegate consider a proposal to include cosmetic preparations and/or domestic preparations containing phenol, 2-amino- in Appendix C.

The delegate's reason for referring this scheduling proposal to the ACCS was that o-aminophenol is a hair dye ingredient with the following toxicological issues: acute toxicity, mutagenicity and sensitisation potential. The NICNAS recommendation is 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:

- Noting that the toxicological data on o-aminophenol is limited, and the NICNAS assessment is based on read-across from available data on the isomers p- and m-aminophenol, does the ACCS support the contention that the mutagenic potential warrants stringent controls over use in cosmetics and consumer products?
- What weight should be given to the equivocal evidence of sensitisation potential?
- In the light of insufficient information on carcinogenicity, what weight should be given to the range of positive and negative studies on genotoxicity?
- Does the ACCS consider that including o-aminophenol in Schedule 6 or 7, or a specific entry in Appendix C is the best option for controlling its use in consumer products and cosmetics, including hair dyes?
- What name should be used for any schedule entry – 2-hydroxyaniline, o-aminophenol, or 1-hydroxy-2-aminophenol?
- Is there a need for specific entries in Appendices E & F?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *phenol, 2-amino*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=865.

Scheduling status

Phenol, 2-amino is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One submission was received. The submission indicated that the substance is being phasing out of use in Australia and this is most likely due to the inclusion of the substance in the EU banned list.

ACCS advice to the delegate

The ACCS recommended that phenol, 2-amino- does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate notes the advice from the ACCS that the toxicity profile of o-aminophenol is partly based on 'read-across' from other isomers. It has a HSIS Cat 3 mutagenicity categorisation (*in vitro* positive but negative *in vivo*) supporting the ACCS advice that evidence of its potential mutagenicity is too weak to support any scheduling actions. The delegate notes that there are some international restrictions on its use in cosmetic products but that ACCS advice is that such use is unlikely in Australia. Based on the use pattern and toxicity profile the substance, the ACCS considered there were no public health issues to be addressed via scheduling. The delegate therefore accepts the ACCS advice that a schedule listing of o-aminophenol in the SUSMP is not required.

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; and (c) the toxicity of a substance.

1.10 PHENYLENEDIAMINES

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To review the generic listings for phenylenediamines in Schedule 6 and Appendices C, E and F, taking into consideration recommendations contained in NICNAS IMAP reports relating to the isomers 1,2-benzenediamine, 1,3-benzenediamine and 1,4-benzenediamine-N-phenyl. This will include consideration of broadening the scope of the generic phenylenediamine listing to include aryl as well as alkyl derivatives.

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

On 24 April 2014, NICNAS, under its IMAP programme, requested that the delegate consider a proposal to amend the phenylenediamine Schedule 6 group entry to exclude 1,2-benzenediamine, 1,3-benzenediamine and 1,4-benzenediamine-N-phenyl from this entry and create a new Appendix C entry for hair dye and/or eyelash and eyebrow tinting preparations containing these substances.

The delegate's reason for referring this scheduling proposal to the ACCS was that there are existing generic SUSMP entries for phenylenediamines *and their alkyl derivatives not elsewhere specified in the schedules* in Schedule 6 and Appendices C, E and F. The Schedule 6 entry exempts preparations for dyeing hair and eyelash/eyebrow when labelled with warning statements for skin irritation and eye damage, while the Appendix C entry precludes use in preparations for skin colouration and dyeing eyelash/eyebrow (except when in Schedule 6).

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the NICNAS IMAP reports have raised issues that require amendment to the existing entries for PHENYLENEDIAMINES in Schedule 6, or Appendices C, E and F? Specifically, is there a requirement to list any of the three referred compounds as separate entries from the generic one or separately list the 1,2- and 1,3- isomers in Appendix C?
- Is the existing generic entry in Schedule 6 and Appendices E & F sufficiently clear, given that it exempts any hair dye and eyelash/eyebrow dyeing preparations containing a phenylenediamine when labelled with the prescribed warning statements? The scheduling history of this generic entry is quite complex.
- Is the existing generic entry in Appendix C sufficiently clear, given that it prevents use of any phenylenediamine in skin colouration preparations, but also prevents use in eyelash/eyebrow dyeing preparations, *except when covered by the Schedule 6 entry (which provides an exemption for appropriately labelled preparations)*?
- Noting an issue raised that the current wording of the Appendix C entry that precludes use in skin colouration preparations may not be interpreted in some jurisdictions to cover tattooing preparations used by intradermal injection, is there a need to amend the Appendix C entry to specifically include preparations for skin tattooing?
- Is the mutagenicity potential for the 1,2- and 1,3- isomers (but not the N-phenyl derivative) sufficient reason to prevent their use in all hair dye and eyelash/eyebrow dyeing preparations, by creating a separate entry in Appendix C banning these uses?
- Does the ACCS support the proposed broadening of the generic entries to include N-aryl derivatives, to capture the referred N-phenyl in the generic entry? The wording would then become: PHENYLENEDIAMINES, *including alkylated and arylated derivatives not elsewhere specified in these schedules*.
- Given the sensitising potential of the three compounds, are additional warning statements needed to specifically address this toxic endpoint, or are the existing warning statements (intended to cover sensitisation potential) adequate?
- Considering the mutagenicity potential for the 1,2- and 1,3- isomers, are there any other types of preparations available to the public that would require inclusion in a Schedule 6 (or 7?) entry?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment reports for *1,2-benzenediamine; 1,2-benzenediamine, dihydrochloride; 1,3-benzenediamine; 1,3-benzenediamine, dihydrochloride; and 1,4-benzenediamine, N-phenyl and a salt*. These reports are publicly available on the NICNAS website:

- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=848,

- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=909,
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=832,
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=910 and
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=893.

Scheduling status

These substances are not specifically scheduled. As these substances belong to phenylenediamine chemical group, the phenylenediamine Schedule 6 and Appendix C, E and F entries are applicable.

SCHEDULE 6

PHENYLENEDIAMINES and alkylated phenylenediamines not elsewhere specified in these Schedules:

(a) in preparations packed and labelled for photographic purposes;

(b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, “Do not discard testing solutions into the pool";

(c) in hair dye preparations except 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 irritation 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 1.5 mm in height; or

(d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING - This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and 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 1.5 mm in height.

APPENDIX C

†PHENYLENEDIAMINES in preparations for skin colouration and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

APPENDIX E

Poisons	Standard statements
Phenylenediamines and alkylated phenylenediamines · in hair dyes.	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.
· in other preparations.	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). G1 - Urgent hospital treatment is likely to be needed. (Note – the words 'at once' to be added to instruction A). G3 - If swallowed, do NOT induce vomiting. E1 - If in eyes wash out immediately with water. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

APPENDIX F

Poisons	Warning statements	Safety direction
Phenylenediamines and alkylated phenylenediamines · in hair dyes.	21. WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dying eyelashes or eye brows; to do so may be injurious to the eye.	
· in preparations other than hair dyes.		1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

Scheduling history

In January 1955, the Committee on Poisons Schedules (CPS) decided to list phenylene toluene and other alkylated benzene diamines in Schedule 2. At that time Schedule 2 substances were considered to be poisons, the sale of which was restricted to certain specified categories of vendors and which were subject to identical packing and labelling requirements to those of Schedule 1 but which were not required to be entered in a poisons register.

In March 1980, the PSC decided to delete the Schedule 6 aromatic amines entry and amend the Schedule 6 phenylene diamines entry to include alkylated phenylene diamines.

In May 1985, the PSC noted that a number of phenylene diamines in Schedule 6 listing were individually listed as well as being included in the general entry for phenylene diamines. The PSC agreed that the individual entries were not required in addition to the general entry for phenylene diamines and decided to delete the individual entries. The PSC agreed that no change was required to the Schedule 2 phenylene diamines entry.

In August 2000, the NDPSC agreed to exempt hair dye products containing phenylenediamines or toluenediamines from scheduling, conditional upon specified labelling.

In February and June 2004, the NDPSC considered the outcomes of investigations into incorrectly packed and labelled eyelash/brow tints containing phenylenediamines/toluenediamine and in October 2004, the NDPSC agreed to foreshadow amendments to prohibit use for eyelash/brow tinting. This proposal was varied by the February 2005 NDPSC meeting which instead agreed to foreshadow two options: to allow either salon use only, or all domestic use, of these eyelash/brow tints as Schedule 6 products (when compliant with the specified labelling).

In June 2005, the NDPSC concluded that the potential risk of causing a strong allergic response in a small number of individuals could be minimised through appropriate labelling. The NDPSC therefore agreed to that eyelash/brow tints were Schedule 6 poisons when appropriately labelled.

In June 2006, the NDPSC considered a request for flexibility in applying the mandatory labelling for eyelash/brow tints containing phenylenediamine and toluenediamine. The NDPSC indicated that, as the main risk was sensitisation, which in this case did not demonstrate a clear dose response, strong label warnings were required before such products could be available as Schedule 6. As there was a risk of separation of an outer pack from the immediate container, it was appropriate that all mandatory labelling continued to be applied to the immediate container, regardless of pack size. That the Schedule 6 warning statement would need to be applied, whether the use was domestic or industrial, or the product would default to Appendix C. The NDPSC further confirmed that the introduction to both Appendix E and F provided sufficient flexibility to allow for variation of product use and formulation.

In February 2007, the NDPSC considered the labelling requirements for single use composite pack hair preparations, including those containing phenylenediamines or toluenediamine, in view of amending various references to ‘hair dyes’ to ‘hair preparations’. The NDPSC decided not to amend these references as there was potential for inadvertent capture of products for non-dying use patterns.

In February 2008, the NDPSC considered the scheduling of phenylenediamine and toluenediamine in eyelash/brow tints including restricting non-professional supply to ≤ 5 mL and limiting non-professional supply to ‘complete kit’ forms (i.e. all reagents). The NDPSC agreed that it was not appropriate to address separate supply of a developer for eyelash/brow tinting through the scheduling process as there was little evidence of an actual public health risk from products not being sold in ‘complete kit’ form. The NDPSC also agreed that there was little evidence to support a pack size restriction on the availability of eyelash/brow tints containing phenylenediamine / toluenediamine.

Pre-meeting public submissions

No submissions have been received.

ACCS advice to the delegate

The ACCS recommended that:

- the current Schedule 6 phenylenediamine group entry be amended to include arylated derivatives;

- a new Appendix C entry be created for skin colouration (including tattooing), hair dye, eyelash and eyebrow tinting preparations containing 1,2-benzenediamine and 1,3- benzenediamine; and
- appropriate Appendix E and F statements for phenylenediamines are required.

The ACCS recommended an implementation date of 1 February 2015 for the Appendix C new entry and the amendment. The ACCS recommended an implementation date of 1 July 2015 for the Schedule 6 amendment.

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

The reasons for the recommendation comprised the following:

- 1,2 and 1,3- phenylated diamines genotoxicity and carcinogenicity.
- Arylated phenylenediamines risk of sensitisation can be mitigated by appropriate labelling.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The scheduling of the phenylenediamines is complex. It uses a combination of listing in Appendix C, to restrict their use in certain types of dye products where the risks of skin/eye irritancy are unacceptable (skin colouration and dyeing of eyebrows and eyelashes), and listing in Schedule 6 for hair dyes and other permitted products where label warning statements can provide appropriate protection to product users. In considering the current recommendations in the five NICNAS IMAP reports, the delegate accepts the advice of the ACCS that further restrictions need to be placed on the use of two of the phenylenediamines with highest mutagenic potential, and that the Appendix C entries be broadened to ensure that the prohibition of their use for skin colouration includes use in tattooing. It is also proposed to broaden the Schedule 6 generic entry so that it capture both alkyl and aryl derivatives of phenylenediamine.

Accordingly, the delegate's interim decision is to make relevant amendments to both the Schedule 6 generic entry for phenylenediamines, to broaden the scope of the current Appendix C entry to include skin tattooing preparations, and to make new listings in Appendix C to restrict all uses of the 1,2- and 1,3- isomers in products used for cosmetic purposes (mainly hair dyes) and skin colouration, where the potential for direct application to human skin exists.

The delegate has determined NOT to adopt ACCS recommendations for inclusion of Schedule 6 sub-clauses that provide an exemption for products listed in Appendix C. The current practice of using a 'dagger symbol' in the stem entry designating substances in the schedules that also have a

listing in Appendix C seems to be a more appropriate mechanism for identifying such additionally restrictive conditions.

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; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

Schedule entry

SCHEDULE 6 – Amendment

†PHENYLENEDIAMINES including alkylated and arylated derivatives not elsewhere specified in these Schedules:

(a) in preparations packed and labelled for photographic purposes;

(b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

(c) in hair dye preparations **except** 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 irritation 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 1.5 mm in height; or

(d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and 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 1.5 mm in height.

APPENDIX C – Amendment

PHENYLENEDIAMINES, including alkylated and arylated derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

APPENDIX C – New entry

1,2-BENZENEDIAMINE in preparations for cosmetic use and skin colouration (including tattooing).

1,3-BENZENEDIAMINE in preparations for cosmetic use and skin colouration (including tattooing).

APPENDIX E - Amendment

Poisons	Standard statement
Phenylenediamines including both alkylated and arylated phenylenediamines · in hair dyes.	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.
· in preparations other than hair dyes.	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). G1 - Urgent hospital treatment is likely to be needed. (Note - the words 'at once' to be added to instruction A). G3 - If swallowed, do NOT induce vomiting. E1 - If in eyes wash out immediately with water. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

APPENDIX F - Amendment

Poisons	Warning statements	Safety direction
Phenylenediamines ~~and~~ including both alkylated and arylated phenylenediamines · in hair dyes.	21. WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dying eyelashes or eye brows; to do so may be injurious to the eye.	
· in preparations other than hair dyes.	28. (Over) (Repeated) exposure may cause sensitisation.	1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

The delegate indicated that implementation of the Appendix C restrictions should be as early as possible, to reinforce the public health implications of allowing any further sale of products with the highest mutagenic potential. **An implementation date of 1 February 2015 for the Appendix C entry** is therefore applicable. For the **Schedule 6 amendment, the delegate has proposed an implementation date of 1 July 2015,** this is to allow for an orderly process of product re-labelling where necessary.

1.11 ROSIN OR COLOPHONY

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To place rosin in Schedule 5 with exemptions at low concentrations.

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

On 23 April 2014, NICNAS, under its IMAP programme, requested that the delegate consider a proposal to include rosin in Schedule 5.

The delegate's reason for referring this scheduling proposal to the ACCS was that while the scheduling of rosins has been previously considered by the NDPSC in 1997 and 1998, with no scheduling action taken, other than to list 'colophony' in Appendix B, NICNAS has again raised the issue of respiratory and skin sensitisation as a reason for developing a new schedule entry. Accordingly, this requires advice from the ACCS.

The delegate asked the ACCS the following questions:

- Does the ACCS support the rejection of previous NDPSC consideration of the health risks associated with rosins and their management by worker health and safety (WHS) authorities?
- If so, is listing in Schedule 5, with appropriate prescribed warning statements in Appendix F, the best way of managing non-occupational exposures to products (specifically solder flux) available to the general public?
- Can the ACCS recommend any cut-off concentration to exempt for a Schedule 5 entry?
- Under what name should the listing be made? Is the term 'ROSIN' sufficient, or should the listing include all the terms used in the NICNAS IMAP report? Should there be a cross-reference to '*colophony*' in the SUSMP index and should the '*colophony*' entry in Appendix B be withdrawn?
- What types of consumer products are likely to be captured by Schedule 5 listing, and what advice does ACCS offer in relation to management of the regulatory impact?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment report for *rosin, hydrogenated rosin and salts*. This report is publicly available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=872.

Scheduling status

Rosin is listed as colophony in Appendix B.

Substance	Date of entry	Reason for listing	Area of use
Colophony	February 1997	b. Use pattern restricts hazard.	7. General 7.4 Flux

Scheduling history

Colophony was considered by the NDPSC in February 1997 and February 1998.

In February 1997, the NDPSC indicated that colophony was well recognised as a skin and respiratory system sensitiser, and at higher concentrations an irritant to skin, the respiratory tract and mucosal surfaces. The allergenicity and irritant properties depend, to some extent, on the composition of the products, and both acid and neutral components have been shown to play a role in sensitisation. The NDPSC noted that the main risk of adverse health effects from colophony exposure would be associated with exposure to fume while using "rosin" cored solders. There appears to be minimal risk of skin contact with "rosin" in the core of these solders because of their physical form. The risk attached to hobby use of these solders is probably much lower but asthmatics and very frequent users could experience adverse health effects. Safety Data Sheets and labels of local products did not adequately warn of health effects. The NDPSC agreed that health warning statements should appear on the product labels and noted that this could be done by reverse scheduling so that colophony could be exempt from scheduling on the condition that the product was labelled with the health warnings. It was also agreed that, because the main concern was with the thermal degradation products in solder, any health warnings should be confined to that type of colophony product.

Pre-meeting public submissions

One submission was received. The submission indicated that there are no restrictions in the EU or the USA for the use of these substances in cosmetics. The submissions requested that the substances be unscheduled.

Summary of ACCS advice to the delegate

The ACCS recommended that a new Schedule 5 entry be created for rosin when packaged for use as a soldering flux or in flux-cored solder. The committee, in addition, recommended appropriate Appendix E and F statements for rosin and a cross-index for colophony be created.

The ACCS recommended an implementation date of 1 July 2015.

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

The reason for the recommendation is:

- Respiratory sensitisation.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate notes, and accepts, ACCS advice that the sensitising potential for rosins warrants inclusion in Schedule 5. The respiratory and skin sensitising potential has been well characterised for uses mainly associated with fumes generated when soldering using rosin-based solder flux and flux-cored solder. The delegate therefore agrees to create a new Schedule 5 entry for rosins, with appropriate warning statements in Appendix F relating to the risks of breathing these fumes. A consequent amendment is the need to delete the current Appendix E entry for colophony, an alternative name for rosins, and to make relevant cross-references in the SUSMP index.

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; and (c) the toxicity of a substance.

SCHEDULE 5 – New entry

ROSIN when packaged for use as a soldering flux or in flux-cored solder.

APPENDIX F, PART 1 – New entry

108. Breathing of solder fumes is harmful and may cause asthma or sensitisation.

APPENDIX F, PART 2 – New Entry

37. Avoid breathing solder fumes.

APPENDIX F, PART 3 – New Entry

Poison	Warning Statement	Standard Direction
Rosin	Breathing of solder fumes is harmful and may cause asthma or sensitisation.	Avoid breathing solder fumes.

INDEX – NEW ENTRY

COLOPHONY

See also ROSIN

APPENDIX B – DELETE ENTRY

COLOPHONY

The delegate indicated that a long implementation time is necessary to allow for orderly relabelling of any affected products therefore an **implementation date of 1 July 2015** is applicable for the scheduling decision.

1.12 TOLUENEDIAMINE

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To amend the Schedule 6 toluenediamine group entry to exempt 1,3-benzenediamine, 2-methyl- from the Schedule 6 entry and create a new Appendix C entry for 1,3-benzenediamine, 2-methyl-

- To amend the Schedule 6 toluenediamine group entry to exempt 1,3-benzenediamine, 4-methyl- and its salts and derivative from this entry and create a new Appendix C entry for hair dye and eyebrow/eyelash tinting preparations containing 1,3-benzenediamine, 4-methyl- and its salts and derivative.
- To amend the Schedule 6 toluenediamine group entry to include nail polish preparations containing toluenediamine.

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

On 23 April 2014, NICNAS, under its IMAP programme, requested the delegate consider a proposal to amend the Schedule 6 toluenediamine group entry to exempt 1,3-benzenediamine, 2-methyl- from the Schedule 6 entry and create a new Appendix C entry for 1,3-benzenediamine, 2-methyl-.

The reasons for the request were:

- systemic acute effects (acute toxicity from oral and dermal exposure). Safe Work Australia's HSIS indicates that this substance is 'Harmful if swallowed' and 'Harmful in contact with skin';
- local effects (skin sensitisation). Safe Work Australia's HSIS notes that this substance 'May cause sensitisation by skin contact'; and
- systemic long-term effects (mutagenicity). Safe Work Australia's HSIS notes that this substance has 'Possible risk of irreversible effects'.

Secondly, NICNAS proposed to amend the current Schedule 6 toluenediamine group entry to exempt 1,3-benzenediamine, 4-methyl from this entry and create a new Appendix C entry for hair dye and eyebrow/eyelash tinting preparations containing 1,3-benzenediamine, 4-methyl-.

The reasons for the request were:

- systemic acute effects - acute toxicity from oral and dermal exposure;
- local effects (skin sensitisation and eye irritation);
- systemic long-term effects - carcinogenicity, genotoxicity and reproductive toxicity; and
- the substance may also cause harmful effects following repeated oral exposure.

Thirdly, NICNAS proposed that the current Schedule 6 toluenediamine group entry be amended to include nail polish preparations containing toluenediamine.

The reasons for this request were:

- systemic acute effects (by the oral, dermal and inhalation route);
- local effects (skin sensitisation and eye irritation); and
- the chemical may also cause harmful health effects following repeated oral exposure.

The NICNAS IMAP programme referred three toluenediamine isomers for scheduling consideration. These isomers are the 2,4 -diamine, 2,5 -diamine and 2,6 -diamine. There are existing generic SUSMP entries for toluenediamine in Schedule 6 and Appendices C, E and F. The Schedule 6 entry exempts preparations for dyeing hair and eyelash/eyebrow when labelled with warning statements for skin irritation and eye damage, while the Appendix C entry precludes use in preparations for skin colouration and dyeing eyelash/eyebrow (except when in Schedule 6).

The NICNAS scheduling proposals for the three isomers are comparable and the delegate has determined that they be considered as a group, addressing possible revision of the current SUSMP entries for toluenediamine.

The delegate asked the ACCS the following questions:

- Does the ACCS consider that the NICNAS IMAP reports have raised issues that require amendment to the existing entries for TOLUENEDIAMINE in Schedule 6, or Appendices C, E and F? Specifically, is there a requirement to list any of the three isomers as separate entries from the generic one?
- Is the existing generic entry in Schedule 6 and Appendices E & F sufficiently clear, given that it exempts any hair dye and eyelash/eyebrow dyeing preparations containing a toluenediamine when labelled with the prescribed warning statements? The scheduling history of this generic entry is quite complex. Are there likely to be any toluenediamines left in the generic entry if it is amended to exclude the 2,4-, 2,5- and 2,6 -isomers?
- Is the existing generic entry in Appendix C sufficiently clear, given that it prevents use of any toluenediamine in skin colouration preparations, but also prevent use in eyelash/eyebrow dyeing preparations, except when covered by the Schedule 6 entry (which provides an exemption for appropriately labelled preparations)?
- Is the mutagenicity potential for the 2,4- and 2,6 -isomers (but not the 2,5 -isomer) sufficient reason to prevent their use in all hair dye and eyelash/eyebrow dyeing preparations, by creating a separate entry in Appendix C banning these uses?
- Is there a need to create a specific amendment to the generic entry to cover the use of the 2,5 -isomer in nail polish preparations, or is a separate entry required for this use?
- Given the sensitising potential of the three isomers, are additional warning statements needed to specifically address this toxic endpoint, or are the existing warning statements (intended to cover sensitisation potential) adequate?
- Considering the mutagenicity potential for the 2,4- and 2,6- isomers, are there any other types of preparations available to the public that would require inclusion in a Schedule 6 (or 7?) entry?
- Are there any other toluenediamines in the current schedules, or is the current wording of the Schedule 6 entry (… not elsewhere specified in these schedules) redundant?

Substance summary

Please refer to the NICNAS IMAP human health Tier II assessment reports for: *1,3-benzenediamine, 2-methyl-; 1,3-benzenediamine, 4-methyl-; 1,3-benzenediamine, 4-methyl-, sulfate; and 1,4-benzenediamine, 2-methyl-*. These reports are publicly available on the NICNAS website:

- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=851;
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=831;
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=936; and
- http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=869

Scheduling status

1,3-benzenediamine, 4-methyl-; 1,3-benzenediamine, 2-methyl-; 1,3-benzenediamine, 4-methyl-, sulfate; and 1,4-benzenediamine, 2-methyl- are not specifically scheduled. As 1,3-benzenediamine, 4-methyl-; 1,3-benzenediamine, 2-methyl-; 1,3-benzenediamine, 4-methyl-, sulfate; and 1,4-benzenediamine, 2-methyl- belong to the chemical group toluenediamine, which is in Schedule 6 and Appendices C, E and F.

SCHEDULE 6

†TOLUENEDIAMINE not elsewhere specified in these Schedules:

(a) in hair dye preparations **except** 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 irritation 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 1.5 mm in height; or

(b) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING - This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and 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 1.5 mm in height.

APPENDIX C

TOLUENEDIAMINE in preparations for skin colouration and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

APPENDIX E

Poisons	Standard statements
Toluenediamine · in hair dyes.	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.

Poisons	Standard statements
· in other preparations.	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). G1 - Urgent hospital treatment is likely to be needed. (Note – the words 'at once' to be added to instruction A). G3 - If swallowed, do NOT induce vomiting. E1 - If in eyes wash out immediately with water. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

APPENDIX F

Poisons	Warning statements	Safety direction
Toluenediamine · in hair dyes.	21. WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dying eyelashes or eye brows; to do so may be injurious to the eye.	
· in other preparations.		1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist.

Scheduling history

In January 1955, the CPS decided to list phenylene toluene and other alkylated benzene diamines in Schedule 2. At that time Schedule 2 substances were considered to be poisons, the sale of which was restricted to certain specified categories of vendors and which were subject to identical packing and labelling requirements to those of Schedule 1 but which were not required to be entered in a poisons register.

In March 1980, the PSC decided to delete the Schedule 6 aromatic amines entry and amend the Schedule 6 phenylene diamines entry to include alkylated phenylene diamines.

In May 1985, the PSC noted that a number of phenylene diamines in Schedule 6 listing were individually listed as well as being included in the general entry for phenylene diamines. The PSC agreed that the individual entries were not required in addition to the general entry for phenylene

diamines and decided to delete the individual entries. The PSC agreed that no change was required to the Schedule 2 phenylene diamines entry.

In August 2000, the NDPSC agreed to exempt hair dye products containing phenylenediamines or toluenediamines from scheduling, conditional upon specified labelling.

In February and June 2004, the NDPSC considered the outcomes of investigations into incorrectly packed and labelled eyelash/brow tints containing phenylenediamines/toluenediamine and in October 2004, the NDPSC agreed to foreshadow amendments to prohibit use for eyelash/brow tinting. This proposal was varied by the February 2005 NDPSC meeting which instead agreed to foreshadow two options: to allow either salon use only, or all domestic use, of these eyelash/brow tints as Schedule 6 products (when compliant with the specified labelling).

In June 2005, the NDPSC concluded that the potential risk of causing a strong allergic response in a small number of individuals could be minimised through appropriate labelling. The NDPSC therefore agreed to that eyelash/brow tints were Schedule 6 poisons when appropriately labelled.

In June 2006, the NDPSC considered a request for flexibility in applying the mandatory labelling for eyelash/brow tints containing phenylenediamine and toluenediamine. The NDPSC indicated that, as the main risk was sensitisation, which in this case did not demonstrate a clear dose response, strong label warnings were required before such products could be available as Schedule 6. As there was a risk of separation of an outer pack from the immediate container, it was appropriate that all mandatory labelling continued to be applied to the immediate container, regardless of pack size. That the Schedule 6 warning statement would need to be applied, whether the use was domestic or industrial, or the product would default to Appendix C. The NDPSC further confirmed that the introduction to both Appendix E and F provided sufficient flexibility to allow for variation of product use and formulation.

In February 2007, the NDPSC considered the labelling requirements for single use composite pack hair preparations, including those containing phenylenediamines or toluenediamine, in view of amending various references to ‘hair dyes’ to ‘hair preparations’. The NDPSC decided not to amend these references as there was potential for inadvertent capture of products for non-dying use patterns.

In February 2008, the NDPSC considered the scheduling of phenylenediamine and toluenediamine in eyelash/brow tints including restricting non-professional supply to ≤ 5 mL and limiting non-professional supply to ‘complete kit’ forms (i.e. all reagents). The NDPSC agreed that it was not appropriate to address separate supply of a developer for eyelash/brow tinting through the scheduling process as there was little evidence of an actual public health risk from products not being sold in ‘complete kit’ form. The NDPSC also agreed that there was little evidence to support a pack size restriction on the availability of eyelash/brow tints containing phenylenediamine / toluenediamine.

Pre-meeting public submissions

One submission was received. The submission indicated that any scheduling change should be aligned with the EU. An extended implementation period of 24 months should be given if the substance is currently in use.

Summary of ACCS advice to the delegate

The ACCS recommended that a new clause be added to the Schedule 6 entry to allow exemption of nail polishes containing the 2,5 isomer when labelled ‘avoid contact with skin’. The committee also recommended that the current Appendix C entry be amended, so that all cosmetic products containing the 2,4-toluenediamine isomers (including hair dyes and eyelash/eyebrow tinters) are prohibited and no longer qualify for inclusion in Schedule 6 or for the exemption clauses.

The ACCS recommended an implementation date of 1 February 2015 for the Appendix C entry. For the amended Schedule 6 entry, the committee recommended an implementation date of 1 July 2015.

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

The reasons for the recommendation comprised the following:

- Genotoxicity and carcinogenicity of 2,4-toluenediamine.
- 2,5-Toluenediamine's risk of skin sensitisation that can be mitigated with appropriate labelling.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The scheduling of the toluenediamines is complex. It uses a combination of listing in Appendix C, to restrict their use in certain types of dye products where the risks of skin/eye irritancy are unacceptable (skin colouration and dyeing of eyebrows and eyelashes), and listing in Schedule 6 for hair dyes and other permitted products where label warning statements can provide appropriate protection to product users. In considering the current recommendations in the four NICNAS IMAP reports, the delegate accepts the advice of the ACCS relating to the need for further restrictions on the use of 2,4-toluenediamine and 2,6-toluenediamine (isomers designated in the NICNAS reports with highest mutagenic potential), and that the Appendix C entries be broadened to ensure that the prohibition of their use for skin colouration includes use in tattooing.

Accordingly, the delegate's interim decision is to make relevant amendments to both the Schedule 6 generic entry for toluenediamines, to broaden the scope of the current Appendix C entry to include skin tattooing preparations, and to make new listings in Appendix C to restrict all uses of the 2,4-isomer in products used for cosmetic purposes (mainly hair dyes) and skin colouration, where the potential for direct application to human skin exists. The delegate notes that the ACCS considered the mutagenic potential of the 2,6-isomer to be equivocal and that there was no recommendation to include this isomer in the Appendix C listing.

The delegate has determined NOT to adopt the ACCS recommendations for inclusion of a Schedule 6 sub-clause that references products listed in Appendix C. The current practice of using a 'dagger symbol' in the stem entry designating substances in the schedules that also have a listing in Appendix C seems to be a more appropriate mechanism for identifying such additionally restrictive conditions. Furthermore, the delegate does NOT accept ACCS recommendations to delete the Schedule 6 sub-clauses that relate to labelling and use in hair dye and eyelash/eyebrow tinting products. Such a recommendation would remove controls over all toluenediamines other than the 2,4-isomer in such products.

The delegate does accept ACCS advice that a new sub-clause be added to the Schedule 6 entry to allow for an appropriate warning statement for nail polish preparations containing the 2,5-isomer.

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; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

Schedule entry

SCHEDULE 6 – Amendment

†TOLUENEDIAMINE not elsewhere specified in these schedules

(a) in hair dye preparations **except** 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 irritation 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 1.5 mm in height; or

(b) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and 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 1.5 mm in height; or

(c) in nail polish preparations containing 2,5-toluenediamine **except** when labelled 'avoid contact with skin'.

APPENDIX C – New entry

2,4-TOLUENEDIAMINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

The delegate indicated that implementation of the Appendix C restrictions should be as early as possible, to reinforce the public health implications of allowing any further sale of products with the highest mutagenic potential. **An implementation date of 1 February 2015 for the Appendix C entry** is therefore applicable. For the **Schedule 6 amendment, the delegate has proposed an implementation date of 1 July 2015**, this is to allow for an orderly process of product re-labelling where necessary.

1.13 1-PROPANAMINIUM COMPOUNDS

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

· Whether 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) and/or 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N(C8-18 and C18-unsatd. Acyl

derivs., inner salts) meet the criteria for inclusion in the generic Schedule 5 and Schedule 6 entries for quaternary ammonium compounds or whether to create a new Schedule 6 and Appendix F entries for 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) and/or 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N(C8-18 and C18-unsatd. Acyl derivs., inner salts).

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

On 13 September 2013, NICNAS, under its New Chemicals programme, requested that the delegate consider creating new Schedule 6 and Appendix F entries for 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) and 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N(C8-18 and C18-unsatd. Acyl derivs., inner salts).

The delegate's reason for referring this scheduling proposal to the ACCS was that the primary use of both compounds will be in leave-on and rinse-off cosmetic products and hair conditioners. Both compounds have a typical toxicological profile of quaternary ammonium compounds, with acute toxicity, skin-eye irritancy and sensitisation potential as the key factors requiring controls via scheduling. The issue that requires ACCS advice is whether the two compounds need individual schedule entries, or whether they are adequately covered by the generic entries for quaternary ammonium compounds in Schedules 5 and 6.

The delegate has raised the following specific questions to the ACCS:

- Are the toxicological profiles of 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) and 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N(C8-18 and C18-unsatd. Acyl derivs., inner salts) comparable with other quaternary ammonium compounds, and are scheduling matters adequately covered by the current Schedules 5 and 6 entries? Note that for the second of these compounds, the toxicological profile has been derived by read-across from an analogue which differs only in the oil source for the fatty acid.
- Are the cut-offs in the current quaternary ammonium entries (Schedule 5 for 5-20% and exemption in less than 5%) appropriate for these two compounds?
- NICNAS has noted that the upper concentration likely to be used in cosmetic and hair conditioner products in Australia is 6%, meaning that if the current quaternary ammonium compound cut-offs are applied, no products containing these two specific compounds are likely to be classified Schedule 6, and most would be either Schedule 5 or exempt from scheduling. Is this consistent with NICNAS advice that listing in Schedule 6 is the preferred option, with strong warning statements about skin/eye irritation and sensitisation potential?
- If separate schedules are recommended for either compound, should they be listed with the above chemical names, or their INCI names (stearoxypropyltrimonium chloride and babassuamidopropyl betaine, respectively)?

Substance summary

Please refer to the NICNAS assessment reports for *stearoxypropyltrimonium chloride* and *1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts (INCI name: Babassuamidopropyl Betaine*. These reports are publicly available on the NICNAS website:

- http://www.nicnas.gov.au/__data/assets/pdf_file/0013/10624/STD1336FR.pdf
- http://www.nicnas.gov.au/__data/assets/word_doc/0014/6800/LTD1578FR.docx

Scheduling status

Neither 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) nor 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N (C8-18 and C18-unsatd. acyl derivs., inner salts) are specifically scheduled. The substances are quaternary ammonium compounds which are listed in Schedules 5 and 6, and also included in Appendix E. Some quaternary ammonium compounds, such as benzalkonium chloride are specifically listed in Schedules 5 (more than 1% and 10% or less), 6 and appendix E.

SCHEDULE 5

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

(a) when separately specified in these schedules;

(b) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

(c) in preparations containing 5 per cent or less of such quaternary ammonium compounds.

SCHEDULE 6

QUATERNARY AMMONIUM COMPOUNDS **except**:

(a) when separately specified in these Schedules;

(b) when included in Schedule 5;

(c) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

(d) in preparations containing 5 per cent or less of such quaternary ammonium compounds.

APPENDIX E

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

Poisons	Standard statements
· 20 per cent and below	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E2 - If in eyes, hold eyelids apart and flush the eyes continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.
· in pressurised spray paints	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E2 - If in eyes, hold eyelids apart and flush the eyes continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes. G6 – If sprayed in mouth, rinse mouth with water.

Scheduling history

Neither 1-Propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) nor 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N (C8-18 and C18-unsatd. acyl derivs., inner salts) have been previously considered for scheduling; therefore, scheduling history is not available.

The following is the scheduling history for quaternary ammonium compounds.

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

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

In November 1998, the NDPSC decided to amend the Schedules 5 and 6 entries to exempt dialkyl quaternary ammonium compounds where the alkyl groups are derived from tallow or hydrogenated tallow or similar alkyl chain length sources from these listings.

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

Pre-meeting public submissions

One submission was received. The submission indicated that technically, both compounds are quaternary ammonium compounds and would be captured under the current schedule entry for quaternary ammonium compounds. The submission noted that the toxicity of 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 and C18-unsatd. acyl) derivs., inner salts is significantly different from other quaternary ammonium compounds and warrants separate consideration. The submission stated that the current scheduling requirements for quaternary

ammonium compounds are too restrictive to apply to babassuamidopropyl betaine and other amidopropyl betaines derived from fatty acids (with carbon chain length of C6-C20) and these substances should be exempt from scheduling.

Summary of ACCS advice to the delegate

The ACCS recommended that 1-propanaminium, N,N,N-trimethyl-3-(octadecyloxy)-, chloride (1:1) and 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N(C8-18 and C18-unsatd. Acyl derivs., inner salts) meet the factors of the SPF for including them in the generic Schedule 5, Schedule 6 and Appendix E entries for quaternary ammonium compounds. A separate listing in the Schedules is therefore not required for these substances.

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, and accepts, ACCS advice that the toxicological profiles of the three substances referred in the NICNAS report are sufficiently similar to other quaternary ammonium compounds covered by the generic listing in Schedules 5 and 6, and that separate listings are therefore not required. This interim decision includes a determination that the current cut-offs from Schedule 6 to Schedule 5 (20%) and to exempt (5%) remain appropriate for these three substances.

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

1.14 2-BUTENEDIOIC ACID (2E)-, DI-C12-15-ALKYL ESTERS

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To create a new Schedule 6 and Appendix F entries for preparations containing 10% or more of 2-butenedioic acid (2E)-, di-C12-15-alkyl esters.

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

On 13 September 2013, NICNAS, under its New Chemicals programme, requested that the delegate consider including preparations containing 10% or more of 2-butenedioic acid (2E)-, di-C12-15-alkyl esters in Schedule 6 and Appendix F. The reason for this recommendation was that the substance is a skin sensitiser that meets the, SPF Schedule 6 criteria.

The delegate's reason for referring this scheduling proposal to the ACCS was that, while the NICNAS assessment report proposed listing this new chemical in Schedule 6, ACCS advice is

needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use as a skin conditioning agent/emollient in cosmetic products (e.g. in leave-in and rinse-off cosmetics) at concentrations up to 10%.

The delegate asked the ACCS the following questions:

- The main features of the toxicity profile of this chemical are low acute toxicity (LD_{50} >2000mg/kg; no evidence of skin/eye irritancy) but some evidence of sensitisation potential (positive at 100%, but negative at 75%). Does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and does the ACCS support the proposed low cut-off concentration to exempt at 10%? Are different cut-offs required for different product categories?

- If scheduled, what name should be used in the listing – the INCI name of Di-C12-15 Alkyl fumarate, or the chemical name 2-Butenedioic acid (2E)-, di-C12-15-alkyl esters?

- The basis for the NICNAS scheduling recommendation is the estimated risk of sensitisation associated with its use in cosmetics at up to 10%. Is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 6? Are Appendix E & F statements required?

Substance summary

Please refer to the NICNAS assessment report for *2-butenedioic acid (2E)-, di-C12-15-alkyl esters (INCI Name: di-C12-15 alkyl fumarate)*. This report is publicly available on the NICNAS website:

- http://www.nicnas.gov.au/__data/assets/word_doc/0004/5539/LTD1509-Final-public-report.docx

Scheduling status

2-Butenedioic acid (2E)-, di-C12-15-alkyl esters is not specifically scheduled.

Scheduling history

2-Butenedioic acid (2E)-, di-C12-15-alkyl esters has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

One submission was received. The submission indicated that the substance should remain unscheduled.

Summary of ACCS advice to the delegate

The ACCS recommended that 2-butenedioic acid (2E)-, di-C12-15-alkyl esters does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;

- Public submissions received;

- ACCS advice;

- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors;
- Other relevant information.

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient 2-butenedioic acid (2E)-, di-C12-15-alkyl esters does not require scheduling. The delegate notes that sensitisation potential is the toxicological finding that could justify inclusion in the schedules, and that the ACCS has made recommendations at this and previous meetings that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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

1.15 2-PENTYL CYCLOPENTANOL

Scheduling proposal

The ACCS considered the following proposal referred by the the delegate for advice:

- To create a new Schedule 5 and Appendix F entries for 2-pentyl cyclopentanol with appropriate concentration cut-off to exempt for preparations with low concentrations.

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

On 13 September 2013, an application was received requesting that the delegate consider a proposal to include 2-pentyl cyclopentanol in Schedule 5 and Appendix F. The reasons for this request are that the substance has a slight to moderate skin and eye irritation potential.

The delegate's reason for referring this scheduling proposal to the ACCS is that ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its use in low concentrations in fragrances, cosmetics and household cleaners.

The delegate asked the ACCS the following questions:

- Given the relatively moderate toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use as a fragrance in cosmetic and household cleaning products containing up to 5%, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt? Are different cut-offs required for different product categories?
- Noting that the pure chemical is a slight-moderate skin/eye irritant, but not a sensitiser, and there is limited information on these toxicities at the low concentrations proposed for consumer products, is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 5? Are Appendix E & F statements required?

Substance summary

2-Pentyl cyclopentanol is intended to be used as a component of fragrances in a variety of cosmetic and household cleaning products at concentrations up to 5%.

Acute toxicity

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

TOXICITY	*SPECIES*	*2-PENTYL CYCLOPENTANOL*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	>2000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Irritant	
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation	Guinea pig	Non-sensitiser	

Repeated dose toxicity

No information was provided.

Mutagenicity

2-Pentyl cyclopentanol was found to be non-mutagenic in a bacterial reverse mutation assay and was not clastogenic in an in vitro mammalian chromosome aberration test.

Genotoxicity

2-Pentyl cyclopentanol was found to be non-genotoxic in *in vitro* mammalian chromosome aberration.

Neurotoxicity

No information was provided.

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 ≤5% concentration) through the use of the household cleaning products and rinse-off and leave-on

cosmetic and personal care 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

2-Pentyl cyclopentanol is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

One submission was received, which indicated that the substance should remain unscheduled.

Summary of ACCS advice to the delegate

The ACCS recommended that 2-pentyl cyclopentanol does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient 2-pentyl cyclopentanol does not require scheduling. The delegate noted evidence of mild skin/eye irritancy potential at high concentrations, but that, based on studies with limited numbers of treated subjects, there appeared to be no evidence of sensitisation potential. The ACCS has made recommendations at this and previous meetings that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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.

1.16 2-PROPYL HEPTANENITRILE

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To create a new Schedule 6 and Appendix F entries for preparations containing 2-propyl heptanenitrile with appropriate low concentration cut-off for low concentration preparations.

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

Scheduling application

On 13 September 2013, an application was received requesting that the delegate consider a proposal to include 2-propyl heptanenitrile in Schedule 6 and Appendix F. The reasons for this request are that the substance has moderate to high acute oral toxicity and a slight to moderate skin irritant potential.

The delegate's reason for referring this scheduling proposal to the ACCS was that ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its use in low concentrations in fragrances, cosmetics and household cleaners.

The delegate asked the ACCS the following questions:

- Given the relatively moderate toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use as a fragrance in cosmetic and household cleaning products containing up to 0.5%, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt 2-propylheptanenitrile from scheduling? Are different cut-offs required for different product categories?
- Noting that the pure chemical is a slight-moderate skin/eye irritant, but not a sensitiser and there is limited information on these toxicities at the low concentrations proposed for consumer products, is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 6, or is it more consistent with SPF criteria for listing in Schedule 5? Are Appendix E & F statements required?

Substance summary

2-Propyl heptanenitrile is intended to be used as a component of fragrances for a variety of cosmetic and domestic products at concentrations up to 0.5%

Acute toxicity

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

TOXICITY	*SPECIES*	*2-PROPYL HEPTANENITRILE*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	2000	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Irritant	

TOXICITY	SPECIES	2-PROPYL HEPTANENITRILE	SPF CLASSIFICATION
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation	Guinea pig	Non-sensitiser	

Repeated dose toxicity

No information was provided.

Mutagenicity

2-Propyl heptanenitrile was found to be non-mutagenic in a bacterial reverse mutation assay and was not clastogenic in an *in vivo* mouse micronucleus test.

Genotoxicity

2-Propyl heptanenitrile was found to be non-genotoxic in an *in vivo* mouse micronucleus assay.

Neurotoxicity

No information was provided.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

At the proposed usage concentration acute toxicity effects are not expected. The repeated dose toxicity effects of the chemical have not been determined. However, exposure is expected to be limited by the low concentration of the notified chemical in end-use products.

International regulations

No information was provided.

Scheduling status

2-Propyl heptanenitrile is not specifically scheduled.

Scheduling history

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

Pre-meeting public submissions

A submission was received. The submission indicated that the substance should remain unscheduled.

Summary of ACCS advice to the delegate

The ACCS recommended that 2-propyl heptanenitrile does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient 2-propyl heptanenitrile does not require scheduling. The delegate noted evidence of mild skin/eye irritancy potential at high concentrations, but that there appeared to be no evidence of sensitisation potential. The ACCS has made recommendations at this and previous meetings that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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

1.17 2,4,7-DECATRIENOIC ACID, ETHYL ESTER

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To create new Schedule 6 and Appendix F entries for 2,4,7-decatrienoic acid, ethyl ester with appropriate cut-off to exempt from scheduling.

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

On 13 September 2013, an application was received requesting that the delegate consider a proposal to include 2,4,7-decatrienoic acid, ethyl ester in Schedule 6 and Appendix E entries. The reasons for this request are that the substance is a slight to moderate skin irritant, a skin sensitiser and a slight eye irritant.

The delegate's reason for referring this scheduling proposal to the ACCS is that ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use in low concentrations in fragrances, cosmetics and household cleaners. The delegate asked the ACCS the following questions:

- Given the relatively moderate toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use as a fragrance in cosmetic and household cleaning

products containing up to 1%, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt 2,4,7-decatrienoic acid, ethyl ester from scheduling? Are different cut-offs required for different product categories?

- Noting that the pure chemical is a skin/eye irritant and a potential sensitiser, but there is limited information on these toxicities at the low concentrations proposed for consumer products, is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 6? Are Appendix E & F statements required?

Substance summary

The chemical is intended to be used as a component of fragrances for a variety of cosmetic and household cleaning products at concentrations up to 1%.

Acute toxicity

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

TOXICITY	*SPECIES*	*2,4,7-DECATRIENOIC ACID, ETHYL ESTER*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Irritant	
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation	Guinea pig	Non-sensitiser	

Repeated dose toxicity

No information was provided.

Mutagenicity

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

Genotoxicity

No information was provided.

Neurotoxicity

No information was provided.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

Repeat dose toxicity data are not available for the chemical. However, based on studies conducted on an analogue of an expected major metabolite of the chemical, systemic toxicity is not expected. The main risk associated with use of the chemical in fine fragrances, other cosmetic products and household cleaning products at concentrations up to 1%, is its potential to cause sensitisation by skin contact.

International regulations

No information was provided.

Scheduling status

2,4,7-Decatrienoic acid, ethyl ester is not specifically scheduled.

Scheduling history

2,4,7-Decatrienoic acid, ethyl ester has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

Two submissions were received. The submissions indicated that the substance should remain unscheduled.

Summary of ACCS advice to the delegate

The ACCS recommended that 2,4,7-decatrienoic acid, ethyl ester does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient 2,4,7-Decatrienoic acid, ethyl ester does not require scheduling. The delegate notes that sensitisation potential is the toxicological finding that could justify inclusion in the schedules, and that the ACCS has made recommendations at this and previous meetings that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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

1.18 3-HEXANONE, 2-METHYL-, OXIME

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To create new Schedule 6 and Appendix F entries for preparations containing 3-hexanone, 2-methyl-, oxime.

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

On 13 September 2013, an application was received requesting that the delegate considers a proposal to include 3-hexanone, 2-methyl-, oxime in Schedule 6 and Appendix F. The reasons for this request are that the substance has moderate to high acute oral toxicity, skin sensitisation potential, slight eye irritation and slight to moderate skin irritation potential.

The delegate's reason for referring this scheduling proposal to the ACCS was that ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use in low concentrations in fragrances, cosmetics and household cleaners.

The delegate has asked the following specific questions to the ACCS:

- Given the relatively moderate toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use as a fragrance in cosmetic and household cleaning products containing up to 0.5%, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt? Are different cut-offs required for different product categories?

- Noting that the pure chemical has moderate acute toxicity (LD_{50} 200 - 2000 mg/kg), is a slight-moderate skin/eye irritant and a potential sensitiser, but there is limited information on these toxicities at the low concentrations proposed for consumer products, is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 6, or is it more consistent with the factors in the Scheduling Policy Framework for listing in Schedule 5? Are Appendix E & F statements required?

- Does the fact that estimates of repeated dose toxicity are based on studies with an unidentified structural analogue impact on the scheduling recommendation?

Substance summary

3-Hexanone, 2-methyl-, oxime is intended to be used as a component of fragrances for a variety of cosmetic and domestic products at concentrations up to 0.5%.

Acute toxicity

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

TOXICITY	*SPECIES*	*3-HEXANONE, 2-METHYL-, OXIME*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	200 - 2000	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Irritant	
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation	Guinea pig	Sensitiser	

Repeated dose toxicity

No repeated dose toxicity data were provided for the chemical. However, a NOAEL of 25 mg/kg bw/day was established in a 13-week oral toxicity study (administration via drinking water) of a structurally similar analogue chemical in rats, based on effects on the hematopoietic system at higher concentrations.

Mutagenicity

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

Genotoxicity

No information was provided.

Neurotoxicity

No information was provided.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

A significant risk associated with use of the chemical in fine fragrances, other cosmetic products and household products at concentrations up to 0.5%, is its potential to cause sensitisation by skin contact.

International regulations

No information was provided.

Scheduling status

3-Hexanone, 2-methyl-, oxime is not specifically scheduled.

Scheduling history

3-Hexanone, 2-methyl-, oxime has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

Two submissions were received. Both submissions indicated that the substance should remain unscheduled. If the substance, however, requires a schedule listing, therapeutic preparations containing the substance should be exempted from scheduling.

Summary of ACCS advice to the delegate

The ACCS recommended that 3-hexanone, 2-methyl-,oxime does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient 3-hexanone, 2-methyl-, oxime does not require scheduling. The delegate notes that sensitisation potential is the toxicological finding that could justify inclusion in the schedules, and that the ACCS has made recommendations at this and previous meetings that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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

1.19 N-HYDROXY OCTANAMIDE

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To consider listing N-hydroxy octanamide in an appropriate Schedule with appropriate cut-off to exempt from scheduling for preparations with low concentrations.

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

On 13 September 2013, NICNAS, under its New Chemicals programme, requested that the delegate consider a proposal to include the substance in appropriate schedule. The reason for this request is that the repeat dose toxicity data indicate the substance presents a moderate hazard from repeated use and a moderate risk of producing irreversible toxicity.

The delegate's reason for referring this scheduling proposal to the ACCS was that advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use in low concentrations as a chelating agent in cosmetic and personal care products.

The delegate asked the ACCS the following questions:

- Given the relatively minor toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use in cosmetic and personal care products containing up to 0.3%, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt N-hydroxy octanamide from scheduling?

- If scheduled, what name should be used in the listing – the INCI name of CAPRYLHYDROXAMIC ACID, or the chemical name N-HYDROXY OCTANAMIDE?

- Noting that the pure chemical has a very low acute toxicity and no evidence of skin/eye irritancy or sensitisation potential, it does not appear to meet any of the factors in the SPF for scheduling. However, the NICNAS report notes that it has the haematological effects expected of a hydroxamic acid derivative in a repeated dose 90-day rat study with a no observed adverse effect level (NOAEL) of 50 mg/kg bw/d. The NICNAS recommendation for scheduling appears to be based on a relatively low estimate of the Margin of Exposure (MoE 42-71), calculated conservatively on an assumption of 100% absorption from dermal exposures.

Substance summary

Please refer to the NICNAS New Chemicals assessment report for *octanamide, N-hydroxy- (INCI Name: Caprylhydroxamic acid)*. This report is publicly available on the NICNAS website: www.nicnas.gov.au/__data/assets/word_doc/0005/6773/LTD1543FR.docx.

Scheduling status

N-hydroxy octanamide is not specifically scheduled.

Scheduling history

N-hydroxy octanamide has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

Two submissions were received. Both submissions indicated that the substance does not require to be scheduled.

Summary of ACCS advice to the delegate

The committee was unable to make a scheduling recommendation due to insufficient toxicological data, particularly repeat-dose studies, for the notified chemical.

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 was unable to provide scheduling advice due to the paucity of repeated-dose toxicity data. The toxicological profile (although very limited) includes the potential for hydrolysis to hydroxamic acid and for systemic toxicity (haematotoxicity) to occur on repeated exposure. Hydroxamic acid is also listed as having carcinogenic potential (Class 3; limited evidence). Hydroxamic acid is not listed in any Schedule of the SUSMP. Other aspects of its toxicological profile suggest low toxicity that would not meet SPF criteria for listing in any schedule, nor is it classifiable as Hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

The primary reason for the NICNAS recommendation to schedule caprylhydroxamic acid relates to estimates of an unacceptably low MOE associated with its use in cosmetic products. The submissions pointed out that the MOE of 43 was calculated using very conservative assumptions, including 100% dermal bioavailability and exposure via multiple daily product use at the upper level of concentration (0.5%) used in such products. The delegate notes that the NICNAS MOE estimates used methodology recommended in the EU *Scientific Committee on Consumer Safety' (SCCS's) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation*. The MOE estimate would increase to 71 using the same assumptions, but an upper concentration of 0.3% as indicated by producers of cosmetic products on the Australian market. The submissions also pointed out that there are no international restrictions on the use of caprylhydroxamic acid in cosmetics, despite its wide use.

In the absence of a clear scheduling recommendation from the ACCS, and taking into consideration the points made above, the interim decision of the delegate is to NOT include caprylhydroxamic acid in any schedule at this time.

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

1.20 TETRAHYDRO-4-METHYL-2-PHENYL 2H-PYRAN

Scheduling proposal

The ACCS considered the following proposal referred by the delegate for advice:

- To create new Schedule 6 and Appendix F entries for tetrahydro-4-methyl-2-phenyl 2H-pyran with appropriate cut-off to exempt from scheduling.

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

On 13 September 2013, an application was received requesting that the delegate consider a proposal to create new Schedule 6 and Appendix F entries for tetrahydro-4-methyl-2-phenyl 2H-pyran.

The reasons for the request are:

- Skin irritation data indicate tetrahydro-4-methyl-2-phenyl 2H-pyran is a moderate to severe irritant and meets the SPF factors for Schedule 6;
- Skin sensitisation data indicate tetrahydro-4-methyl-2-phenyl 2H-pyran is a moderate skin sensitiser and meets the factors of the SPF for Schedule 6; and
- Based on the available data the chemical is classified as hazardous according to the Safe Work Australia's *Approved Criteria for Classifying Hazardous Substances*. The classification and labelling details are: 'Irritating to skin' and 'May cause sensitisation by skin contact'.

The delegate's reason for referring this scheduling proposal to the ACCS was that ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use in low concentrations in fragrances, cosmetics and household cleaners.

The delegate has raised the following specific issues/questions:

- Given the relatively moderate toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use as a fragrance in cosmetic and household cleaning products containing up to 0.1%, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt? Are different cut-offs required for different product categories?
- Noting that the pure chemical is a slight-moderate skin/eye irritant and a potential sensitiser, but there is limited information on these toxicities at the low concentrations proposed for consumer products, is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 6, or is it more consistent with SPF criteria for listing in Schedule 5? Are Appendix E & F statements required?

Substance summary

Tetrahydro-4-methyl-2-phenyl 2H-pyran will be used as a component of fragrances for a variety of cosmetic and household products, including fine fragrances, cosmetics and household cleaning products at concentrations up to 0.1%.

Acute toxicity

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

TOXICITY	*SPECIES*	*TETRAHYDRO-4-METHYL-2-PHENYL 2H-PYRAN*	*SPF CLASSIFICATION*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Irritant	
Eye irritation	Not provided	Not provided	
Skin sensitisation	Guinea pig	Sensitiser	

Repeated dose toxicity

No information was provided.

Mutagenicity

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

Genotoxicity

No information **was** provided.

Neurotoxicity

No information was provided.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No information was provided.

Observation in humans

No information was provided.

Public exposure

Members of the public may experience repeated exposure to the chemical through use of fine fragrances, cosmetics and household cleaning products at concentrations up to ≤ 0.1%. The repeated dose toxicity effects of the chemical have not been determined; however, based on the low concentration of chemical in end-use products, exposure to the chemical is expected to be limited. In addition, based on the low concentration, the risk of skin and eye irritation is not considered to be unreasonable.

International regulations

No information was provided.

Scheduling status

Tetrahydro-4-methyl-2-phenyl-2H-pyran is not specifically scheduled.

Scheduling history

Tetrahydro-4-methyl-2-phenyl-2H-pyran has not been previously considered for scheduling; therefore, scheduling history is not available.

Pre-meeting public submissions

One submission was received. The submission indicated that the substance does not require a schedule listing.

Summary of ACCS advice to the delegate

The ACCS recommended that tetrahydro-4-methyl-2-phenyl-2H-pyran does not require a schedule listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient tetrahydro-4-methyl-2-phenyl 2H-pyran does not require scheduling. The delegate notes that sensitisation potential is the toxicological finding that could justify inclusion in the schedules, and that the ACCS has made recommendations at this and previous meetings that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the low concentrations likely to be found in consumer products in Australia. There were no other toxicological factors that would justify scheduling. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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