Australian Government
Department of Health
Therapeutic Goods Administration

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

December 2015

(Joint ACMS-ACCS – August 2015)

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

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

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the August 2015 joint meeting of the Advisory Committee on Medicines Scheduling and the Advisory Committee on Chemicals Scheduling (joint ACMS-ACCS#11);
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 28 May 2015 at Consultation: Invitation for public comment - ACCS meeting and joint ACCS/ACMS meeting, July 2015.

Edited versions of these public submissions received in response to this invitation were published on 1 October 2015 at Public submissions on scheduling matters.

Interim decisions

The delegates' interim decisions on recommendations by the joint ACMS-ACCS #11 were published on 1 October 2015 at Reasons for scheduling delegate's interim decisions and invitation for further comment for the ACCS#14 and ACCS/ACMS#11. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions.

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

Edited versions of valid public submissions received in response to the interim decisions were published on 1 October 2015 and are available at Public submissions on scheduling matters.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either, confirming, varying or setting aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2015).

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the Poisons Standard are published electronically on ComLaw as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the Poisons Standard on ComLaw, is available at: The Poisons Standard (the SUSMP).

Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
CAS	Chemical Abstract Service

Abbreviation	Name
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	*Freedom of Information Act 1982*
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name

Abbreviation	Name
ISO	International Standards Organization
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])

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

Abbreviation	Name
SVT	First aid for the solvent prevails
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

Contents

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

1. Scheduling proposals referred to the August 2015 joint meeting of the Advisory Committee on Medicines Scheduling and Advisory Committee on Chemicals Scheduling (ACMS-ACCS#11)

Summary of Delegate's final decisions

Substance	Final decision
METHYLISOTHIAZOLINONE	***Schedule 6—New Entry*** METHYLISOTHIAZOLINONE in leave-on cosmetic products or therapeutic goods intended for leave-on topical application, except in preparations containing 0.01 per cent or less of methylisothiazolinone. ***Appendix F, Part 3—New Entry*** METHYLISOTHIAZOLINONE Warning statement: 28 Safety Direction: (over)(repeated) exposure may cause sensitisation Implementation date: 1 June 2016. ***Schedule 6—Amend Entry*** METHYLISOTHIAZOLINONE except: a) In rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.01 per cent or less of methylisothiazolinone; or b) In other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone Implementation date: 1 October 2017
METHYLCHLOROISOTHIAZOLINONE	***Schedule 6—New Entry*** METHYLCHLOROISOTHIAZOLINONE in leave-on cosmetic products or therapeutic goods intended for leave-on topical application, **except** in preparations containing 0.0015 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total. ***Appendix F, Part 3—New Entry*** METHYLCHLOROISOTHIAZOLINONE

Substance	Final decision
	Warning statement: 28 Safety Direction: (over)(repeated) exposure may cause sensitisation Implementation date: 1 June 2016. ***Schedule 6—Amend Entry*** METHYLCHLOROISOTHIAZOLINONE **except:** a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.0015 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total; or b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total. Implementation date: 1 October 2017.

1.1 Methylisothiazolinone (MI)

Scheduling proposal

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

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

The reasons for the request were:

- Methylisothiazolinone produced skin sensitisation effects in several animal and human studies. Although the potency of these effects varied across the studies, skin sensitisation was sufficiently noted across all the studies to support the Safe Work Australia's HSIS classification of 'May cause sensitisation by skin contact'. Further, the chemical was found to produce an exceptionally high response rate of 11.3% among patients patch tested in Australian dermatological clinics;
- Methylisothiazolinone may also cause systemic acute toxicity (by all route of exposure) and local effects (skin corrosion and the possibility of causing serious damage to eyes);
- Methylisothiazolinone is one of the most commonly used cosmetic preservatives on the Australian market;
- The Cosmetic Ingredient Review (CIR) expert panel concluded that 'MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be non-sensitizing, which may be determined based on a quantitative risk assessment (QRA)' (CIR 2014).
- In 2013, the Scientific Committee on Consumer Safety (SCCS 2013) concluded that "Current clinical data indicate that 100 ppm MI in cosmetic products is not safe for the consumer.

- For leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated.
- For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the view of induction of contact allergy. However, no information is available on elicitation.

The use of the chemical is restricted to a maximum level of 0.01 g/100 g (100 ppm) in both wash-off and leave-on cosmetics in Japan. The use of the chemical in wash-off and leave-on cosmetics in the European Union (EU) and in the Association of Southeast Asian Nations (ASEAN) is restricted to a maximum concentration of 0.01% (Burnett *et al.*, 2010). In the EU, 6.02% of dermatology clinic patients in Germany were found to be sensitised to the chemical even under these restrictions.

The delegate asked the committees the following questions:

- Scheduling of methylisothiazolinone was referred to the July 2014 meeting of the ACCS. Skin sensitisation potential was identified as the key toxicological issue, driving towards listing in Schedule 6 according to SPF criteria. At that time, the ACCS was aware that the EU SCCS and US CIR had considered possible thresholds for leave-on and rinse-off cosmetics containing methylisothiazolinone, below which the risk of skin sensitisation was considered to be acceptable. Both authorities appeared to reach different views on the sensitisation thresholds, and the ACCS advised waiting for a final decision from the US CIR before it could advise to the delegate on possible exemption cut-off(s) from a Schedule 6 entry. The US CIR published its final report in October 2014. The ACCS/ACMS is asked to advise on whether to adopt either the US CIR or EU SCCS sensitisation thresholds as an exemption cut-off from a new Schedule 6 entry for methylisothiazolinone.
- Alternatively, does the ACCS/ACMS support NICNAS advice that Schedule 6 controls are insufficient to protect the public and that consideration be given to listing in Appendix C (Schedule 10) with appropriate exemption cut-offs?
- Noting that the US CIR has specified that the 100 ppm (0.01%) threshold is only suitable for rinse-off cosmetic products, and that a cut-off for leave-on cosmetic products has not been specified, other than that it be based on a product-by-product quantitative risk assessment, the ACCS is asked to advise on whether the EU SCCS proposal for a 15 ppm (0.0015%) for rinse-off cosmetics is a more appropriate general cut-off from Schedule 6.
- Does the ACCS/ACMS advise that any schedule listing for methylisothiazolinone be specific for cosmetic products, as outlined in the NICNAS report? Should different thresholds be proposed for products that are not intended to be directly applied to skin (e.g. cleaning products, deodorisers, antimicrobial gels and sprays)?
- To what extent should the estimates of sensitisation potential derived from animal tests (LLNA and Buehler test) suggest a higher sensitisation threshold than the conclusions of the CIR and SCCS?
- Noting that methylisothiazolinone is used at comparable concentrations in some therapeutic goods, but notably in sunscreen products that are directly applied to the skin, does the ACCS/ACMS advise that a schedule entry should specifically exempt such therapeutic goods or should they be subjected to the same exemption cut-offs as cosmetics?
- Noting that there have been a significant number of reports of allergies associated with the use of methylisothiazolinone in cosmetic and consumer products. It was designated as 'contact allergen-of-the-year' in 2013 by the US Contact Dermatitis Society and there have been Australian case reports of contact dermatitis associated with its use in 'wet wipes'. What weight should be given to the apparent lack of adverse reaction reports associated with its use in therapeutic goods?
- What regulatory impact might be expected in relation to registered AgVet products, given APVMA advice that the maximum concentration of MI is of the order of 0.1-0.2%?

Substance summary

For full substance summary please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) human health Tier II assessment report for 3-isothiazolone, 2-methyl-. This report is publicly available on the NICNAS website.

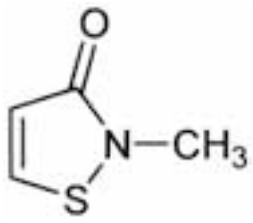

Figure 1. Chemical structure of methylisothiazolinone

Toxicokinetics

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

Acute toxicity

Oral

The chemical had high acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats (Crl:CD®BR strain) was 209 mg/kg bw (235 for male and 183 mg/kg bw for female rats). The chemical (99.7%) was administered as a single dose through gavage at concentrations of 75, 150, 180, 225 and 300 mg/kg bw. Observed sub-lethal effects included passivity, ataxia, scant or no faeces, mucus in faeces, yellow or brown stained anogenital area, red-stained muzzle and/or lacrimation. Additionally, at necropsy reddened intestines and/or stomach mucosa, reddened glandular portion of the stomach, and distended stomachs were observed (CIR, 2010; SCCNFP, 2003).

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

Dermal

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

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

Inhalation

The chemical had high acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC50) for aerosol in rats (Crl:CD®BR strain, 6 animals/group) after four-hour

exposure was 0.11 mg/L. The necropsy showed signs of slight to severe redness in all lobes of the lung in all treatment groups (CIR, 2010).

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

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

Corrosivity

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

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

Eye irritation

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

The chemical (undiluted) was found to be an irritant in a bovine cornea study measuring opacity and permeability. Eye irritation studies using formulations containing the chemical at 100 ppm (body lotion, shampoo and sunscreen) were found non-irritating (CIR, 2010).

Sensitisation

Skin sensitisation

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

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

Following its approval for use as a preservative in cosmetic products in 2005 at a maximum concentration of 100 ppm, several reports have indicated the emergence of the issue of contact allergy to the chemical (see Sensitisation: observation in humans). The permitted use of the chemical at 100

ppm in cosmetic products is approximately 25-fold the permitted concentration of the chemical in the MI/MCI combination (3.75 ppm MI in 15 ppm of MI/MCI).

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

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

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

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

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

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

Observation in humans

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

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

The chemical has been reported to be an emerging and important allergen in both cosmetic and occupational settings in Australia. Baby wipes and facial wipes containing the chemical were reported to be an important cause of hand dermatitis in carers. Facial dermatitis in children was also noted following the use of moist wipes containing the chemical. It was concluded that the continued use of the chemical in baby wipes and facial wipes will lead to increased rates of allergy to these preservatives in adults. The present study also noted three cases of contact allergy as occupational exposure from hand cleansers containing the chemical (Boyapati *et al*., 2013). Based on the results of a series of patch test conducted from 2011-2013, the Medical Journal of Australia reported a significant increase in the incidence of contact dermatitis in adult patients from the use of the baby wipes which contain the chemical (Cahill *et al*., 2014). In this report, the authors highlighted this remarkable rise of contact dermatitis from 3.5% in 2011 to 11. 3% in 2013 among their patient population. The authors also noted that the chemical is now the most common cause of allergic contact dermatitis in their patient population (Cahill *et al*., 2014).

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

Repeated dose toxicity

Oral

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

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

Dermal

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

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

Inhalation

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

In a study conducted in accordance with OECD TG 413, Charles River Crl: CD(SD) BR rats were exposed to an aerosol product containing 14% of the analogue chemical for 13 weeks (0, 0.34, 1.15, or 2.64 mg/m^3, at 6 hours/day, 5 days/week). At the top dose, effects included decreased bodyweight gain and signs consistent with sensory irritation such as chromorhinorrhoea, rhinorrhoea, eye squint, bradypnoea, and dyspnoea. Slight to moderate eosinophilic droplets in the anterior mucosa of the nasal turbinates and slight rhinitis in the lining of the nasal cavity were also reported at the top dose. At the mid-dose, slight incidence of rhinitis was observed. The study authors noted that eosinophilic droplets in the nasal turbinates and rhinitis were possibly reversible responses to upper respiratory tract inflammation. The lowest-observed-adverse-effect-concentration (LOAEC) and no-observed-adverse-effect-concentration (NOAEC) for this study were 2.64 and 1.15 mg/m^3, respectively (SCCS, 2009; US EPA, 1998).

Genotoxicity

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

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

The chemical was reported to be negative in an *in vivo* mouse micronucleus assay (CIR, 2010; SCCNFP, 2003).

Carcinogenicity

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

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

Reproductive and developmental toxicity

The chemical does not show specific reproductive or developmental toxicity.

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

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

Other health effects

Neurotoxicity

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

Scheduling status

Methylisothiazolinone is not specifically scheduled.

Scheduling history

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

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

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

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

Pre-meeting public submissions

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

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

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

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

Summary of ACCS/ACMS advice to the delegates

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

The committee recommended an implementation date of 1 October 2017.

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

The reasons for the recommendations comprised the following:

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

Delegates' interim decision

The key issue driving the need to regulate methylisothiazolinone (MIT) by scheduling is its sensitisation potential. Following initial consideration by the ACCS in July 2014, and the publication of US Cosmetic Ingredients Review (CIR) and EU Scientific Committee on Consumer Safety (SCCS) reviews, the delegates have accepted advice from the joint meeting of the ACCS/ACMS to list methylisothiazolinone in Schedule 6, with exemptions for some types of cosmetics and therapeutic goods containing low concentrations. The delegates noted the increasing prevalence of reported skin sensitisation reactions and determined that the exemption cut-off of 0.0015% proposed by the EU SCCS could be protective for rinse-off cosmetics and therapeutic goods, but not for products applied to the skin and not intended to be washed off. The delegates determined that cosmetic and therapeutic goods intended for application to the skin without washing off posed an unacceptable sensitisation risk and should be included in Schedule 6.

The delegates also determined that when methylisothiazolinone is present in products not intended for direct application to the skin, a higher exemption cut-off (0.1%) could be made in the Schedule 6 entry. The delegates noted that the proposed schedule changes could result in product sponsors needing to re-label, or possibly deciding to re-formulate products using other preservatives, and determined that a reasonably long period be allowed for such actions prior to implementation of the

scheduling decision. The delegates noted that the proposed EU restrictions could already be driving such changes. The delegates noted that some agricultural fungicides, insecticides and external use parasiticides could be affected by the scheduling change, but that most such products would fit within the 0.1% exemption.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Public submissions on the interim decision

Three submissions were received. Two submissions were similar in their comments to the delegates' interim decision. Two submissions supported the decision for leave-on products and had no objections to the implementation date of 24 months. One submission preferred an implementation period of 30 months. All three submissions objected to the decision for a cut-off of 15 ppm for rinse-off cosmetics and topical therapeutic goods, with a main concern being that the MI will not be effective as a preservative at this concentration and proposed a cut-off of 100 ppm to align with international standards. Two submissions also requested to defer the final decision until the release of a European Union SCCS draft report on MI.

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

Delegates' final decision

The delegates note the submissions received in response to publication of the interim decision and have determined to vary the interim decision. The proposed variations address:

1. the wording of clause (a), raising the exemption cut-off from 0.0015% to 0.01%; and
2. the wording of clause (b) to clarify that the proposed exemption cut-off of 0.1% only applies to products that are not intended to be applied directly to human skin;
3. a staged implementation to allow for an earlier date to control all cosmetics and therapeutic goods applied directly to the skin, with a longer period allowed to phase in scheduling that allows for exemptions on only those products intended to be rinsed off.

The reason for raising the cut-off in clause (a) to 0.01% is to align with current international standards for such products. As pointed out in the submissions, the ACCS/ACMS based its advice on an appropriate cut-off for rinse-off preparations on a proposal from the EU SCCS that is yet to be ratified. The submissions included advice that industry has submitted data on quantitative risk assessments (QRA) for different product types that demonstrate an adequate safety profile at up to 0.01% MI for some types of cosmetic products. Should the EU reject these submissions and confirm its proposed cut-off for rinse-off products at 0.0015%, there will be sufficient time prior to the proposed implementation date of 1 October 2017 for the current scheduling decision to be revised accordingly.

The delegates note that the submissions did not object to there being no cut-off to exempt for the Schedule 6 listing of cosmetics and therapeutic goods applied to the skin, but not intended to be

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

washed off, so any such products containing methylisothiazolinone will eventually need to be re-formulated or re-labelled with the signal heading POISON and the appropriate Appendix F warning statement.

The delegates note that it would be possible for restrictions that align with current international standards to be implemented more quickly (say 6 months), and desirable from the point of limiting the potential for sensitizing reactions that have already been documented to occur. Accordingly, the delegates have decided to implement the proposed scheduling changes over two periods. Leave-on products (i.e. those not intended to be rinsed off the skin after application) will need to meet international standard (i.e. contain 0.01% MI or less) or be labelled as Schedule 6 poisons within the proposed six months implementation timeframe. The exemption cut-off for leave-on products will be withdrawn in October 2017, when the Schedule 6 entry will be amended to allow only rinse-off products that meet international standards for MI concentration to qualify for the Schedule 6 exemption. This will achieve the ultimate goal of allowing the Schedule 6 exemption to apply only to products intended to be rinsed off, and therefore present a lower risk of skin sensitization.

The same 1 October 2017 implementation date will also see the introduction of a 0.1% exemption cut-off for products other than cosmetics and therapeutic goods that are not intended to be directly applied to the skin. Both proposed periods of implementation will allow for re-formulation or re-labelling of products that do not meet international standards or the exemption cut-offs proposed by the delegates.

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

While one submission requested an implementation period of 30 months, other submissions accepted that two years should be sufficient to re-label and/or re-formulate products affected by the scheduling decision. The delegates' proposal that the implementation be over two periods, with six months for leave-on cosmetics and therapeutic goods having an exemption cut-off of 0.01%. Other products would remain unscheduled until 1 October 2017, when the amended Schedule 6 entry would apply to all products, with exemptions only for rinse-off cosmetics and therapeutic goods meeting the 0.01% cut-off and other preparations not intended to be applied to the skin having a higher (0.1%) cut-off. One submission raised an issue about whether the two years should start from the date of the final decision, rather than the date of the interim decision. In fact, the implementation date is fixed by the date proposed for publication of the Poisons Standard.

Schedule entry

Schedule 6—New Entry

METHYLISOTHIAZOLINONE in leave-on cosmetic products or therapeutic goods intended for leave-on topical application, except in preparations containing 0.01 per cent or less of methylisothiazolinone.

Appendix F, Part 3—New Entry

Poison	Warning statements	Safety direction
METHYLISOTHIAZOLINONE	28	(over)(repeated) exposure may cause sensitisation

Implementation date: 1 June 2016.

Schedule 6—Amendment

METHYLISOTHIAZOLINONE **except**:

a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.01 per cent or less of methylisothiazolinone; or

b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone

Implementation date: 1 October 2017.

1.2 Methylchloroisothiazolinone (MCI)

Scheduling proposal

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

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

The reasons for the request were:

- the scheduling issue raised in relation to methylchloroisothiazolinone (MCI) have much in common with those raised by methylisothiazolinone (MI) and should be addressed by the ACCS/ACMS after consideration of MI.

Scheduling of the closely related preservative methylisothiazolinone (MI) was first referred to the July 2014 meeting of the ACCS, but this is the first time that methylchloroisothiazolinone (MCI) has been considered. The two preservatives are often used together in a proprietary 1:3 MI/MCI combination.

Skin sensitisation potential has been identified as the key toxicological issue, driving towards listing in Schedule 6 according to SPF criteria. Both the EU SCCS and US CIR have considered possible sensitisation thresholds for leave-on and rinse-off cosmetics containing MI and MCI at various times, although the detailed consideration of MCI is not so recent.

The delegate asked the committee the following questions:

- The ACCS/ACMS is asked to advise on whether to adopt either the US CIR or EU SCCS sensitisation thresholds as an exemption cut-off from a new Schedule 6 entry for methylchloroisothiazolinone. Is there sufficient evidence that MCI may be a more potent sensitiser than MI, and therefore require lower cut-offs? Given the difficulty of discriminating between the sensitisation potential of MCI when used alone, rather than in a MI/MCI combination, should the cut-offs for MCI mirror those recommended for MI?
- Alternatively, does the ACCS/ACMS support NICNAS advice that Schedule 6 controls are insufficient to protect the public and that consideration be given to listing in Appendix C (Schedule 10) with appropriate exemption cut-offs?
- Does the ACCS/ACMS advise that any schedule listing for methylchloroisothiazolinone be specific for cosmetic products, as outlined in the NICNAS report? Should different thresholds be proposed for products that are not intended to be directly applied to skin (e.g. cleaning products, deodorisers, antimicrobial gels and sprays)?
- Noting that methylchloroisothiazolinone is used at comparable concentrations in some therapeutic goods, but notably in sunscreen products that are directly applied to the skin, does the ACCS/ACMS

advise that a schedule entry should specifically exempt such therapeutic goods or should they be subjected to the same exemption cut-offs as cosmetics?

- What weight should be given to the apparent lack of adverse reaction reports associated with the use of MCI in therapeutic goods (Attachment Y)?
- What regulatory impact might be expected in relation to registered AgVet products, given APVMA advice that the maximum concentration of MCI is of the order of 0.1-0.2% (Attachment X)?

Substance summary

For the full NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) human health Tier II assessment report for 3(2*H*)-Isothiazolone, 5-chloro-2-methyl-, refer to the NICNAS website.

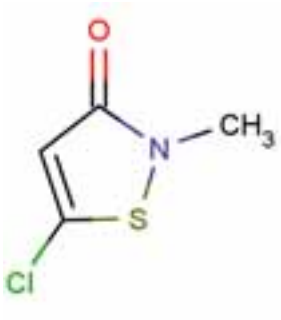

Figure 1: Chemical structure of methylchloroisothiazolinone

Toxicokinetics

Toxicokinetic studies in rats using the chemical (CAS No. 26172-55-4) and its analogue (CAS No. 55965-84-9) show that it is readily absorbed and metabolised. The major metabolic products of the chemical are *N*-methylmalonamic acid (NMMA) and the 3-mercapturic acid conjugate of 3-thiomethyl-*N*-methyl-propionamide. These studies did not report accumulation of the chemical or its metabolites in tissues. The chemical is widely distributed to all tissues in the body, with the highest level in the liver and lowest in the bone. It is eliminated within 24 hours mainly through urine, followed by bile and, finally, faeces.

An *in vitro* human skin absorption study conducted in accordance with OECD Test Guideline (TG) 428 reported maximum potential systemic bioavailability of the chemical as 84.5% of the applied dose (NICNASa; SCCS, 2009).

Acute toxicity

Oral

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

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

Dermal

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

The analogue chemical (MCI/MI, CAS No. 55965-84-9) had high acute toxicity in animal tests using dermal exposure. A study administered in rats using the analogue chemical as 14% reported the LD50

at 141 mg/kg bw for both sexes. A similar study (administered as a 1.5% formulation) in rabbits reported the LD50 as 113 mg/kg bw (CIR, 1992; SCCNFP, 2009).

Inhalation

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

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

Corrosion/Irritation

Skin irritation

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

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

Eye irritation

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

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

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

Sensitisation

Skin sensitisation

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

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

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

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

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

Observation in humans

The chemical has been reported to be a sensitiser in both cosmetic and occupational settings (NICNASa).

Data from multiple research centres conducted between 2010 and 2013 in Europe illustrates a rise in the frequency of sensitisation to the chemical from 4.4 to 8.3%. Further, other pan-European data conducted between 2006 and 2008 illustrates a high prevalence of sensitisation (approximately 2—2.5%) in eczema patients (SCCS, 2013).

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

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

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

Repeated dose toxicity

Oral

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

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

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

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

Dermal

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

Inhalation

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

Genotoxicity

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

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

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

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

Carcinogenicity

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

Reproductive and developmental toxicity

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

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

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

Risk characterisation

Critical health effects

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

Public risk characterisation

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

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

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

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

Occupational risk characterisation

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

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

International regulations

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

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

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

The following exposure standards are identified (Galleria Chemica):

- An exposure limit—TWA of 0.2 mg/m^3 and STEL of 0.4 mg/m^3 was identified in Switzerland.

Scheduling status

Methylchloroisothiazolinone (MCI) is not specifically scheduled.

Scheduling history

Methylchloroisothiazolinone (MCI) has not been previously considered for scheduling.

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

delegates decided to defer further consideration of scheduling methylisothiazolinone pending the publication of the final US CIR decision.

Pre-meeting public submissions

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

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

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

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

Summary of ACCS/ACMS advice to the delegates

The committee recommended methylchloroisothiazolinone be considered a derivative of methylisothiazolinone and be cross referenced with methylisothiazolinone with certain exempt cut-offs.

The committee recommended an implementation date of 1 October 2017.

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

The reasons for the recommendations comprised the following:

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

Delegates' interim decision

As with methylisothiazolinone (MIT), the key issue driving the need to regulate methylchloroisothiazolinone (MCIT) by scheduling is its sensitisation potential. The two substances were considered together by the ACCS/ACMS and this interim decision should be read in conjunction with that for MIT. The delegates accepted the advice from the ACCS/ACMS that MCIT should be listed in Schedule 6, with exemption cut-offs comparable to MIT. The delegates also noted that MCIT is not used as a preservative by itself, but usually in combination with MIT. Accordingly, the delegates determined that the cut-offs applied to MCIT should refer to the combined concentrations.

The delegates noted that the industry request for a cut-off of 7.5 ppm (0.00075 per cent) for leave-on products is not necessary, because of the general exemption (0.001 per cent) provided in Part 1 2(j) of the Poisons Standard.

Delegates' considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;

- Joint ACCS/ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[2];
- Other relevant information.

Public submissions on the interim decision

Two submissions were received. Both submissions supported the delegates' interim decision. One submission proposed re-wording to Appendix F entry for MCI and noted that the proposed exemption cut-off of 0.0015% for products not intended to be applied to the skin may have been an editorial error, if consistency with the scheduling decision was the intent.

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

Delegates' final decision

The delegates note the submissions received in response to publication of the interim decision and have determined to vary the interim decision. The proposed variations address:

1. the wording of clause (b) to clarify that the proposed exemption cut-off should be 0.1% and that this only applies to products that are not intended to be applied directly to human skin;
2. a staged implementation to allow for an earlier date to control all cosmetics and therapeutic goods applied directly to the skin, with a longer period allowed to phase in scheduling that allows for exemptions on only those products intended to be rinsed off.

The delegates note that none of the three submissions raised objection to the proposed exemption cut-off of 0.0015% for methylchloroisothiazolinone (MCI). This is presumably because this concentration currently aligns with international regulations relating to MCI, or there is not much use of MCI in products sold in Australia (despite advice available to the ACCS that there is some use of MCI in some cosmetics and sunscreens).

The delegates note that the submissions did not object to there being no cut-off to exempt for the Schedule 6 listing of cosmetics and therapeutic goods applied to the skin, but not intended to be washed off, so any such products containing MCI will eventually need to be re-formulated or re-labelled with the signal heading POISON and the appropriate Appendix F warning statement.

The delegates note that it would be possible for restrictions that align with current international standards to be implemented more quickly (say 6 months), and desirable from the point of limiting the potential for sensitizing reactions that have already been documented to occur. Accordingly, the delegates have decided to implement the proposed scheduling changes over two periods. Leave-on products (i.e. those not intended to be rinsed off the skin after application) will need to meet international standard (i.e. contain 0.0015% or less MCI in combination with MI) or be labelled as Schedule 6 poisons within the proposed six months implementation timeframe. The exemption cut-off for leave-on products will be withdrawn in October 2017, when the Schedule 6 entry will be amended to allow only rinse-off products that meet international standards for MCI concentration to qualify for the Schedule 6 exemption. This will achieve the ultimate goal of allowing the Schedule 6 exemption to apply only to products intended to be rinsed off, and therefore present a lower risk of skin sensitization.

The same 1 October 2017 implementation date will also see the introduction of a 0.1% exemption cut-off for products other than cosmetics and therapeutic goods that are not intended to be directly applied to the skin. Both proposed periods of implementation will allow for re-formulation or re-

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

labelling of products that do not meet international standards or the exemption cut-offs proposed by the delegates.

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

The delegates' proposal that the implementation be over two periods, with six months for leave-on cosmetics and therapeutic goods having an exemption cut-off of 0.0015%. Other products would remain unscheduled until 1 October 2017, when the amended Schedule 6 entry would apply to all products, with exemptions only for rinse-off cosmetics and therapeutic goods meeting the 0.0015% cut-off and other preparations not intended to be applied to the skin having a higher (0.1%) cut-off. One submission raised an issue about whether the two years should start from the date of the final decision, rather than the date of the interim decision. In fact, the implementation dated is fixed by the date proposed for publication of the Poisons Standard.

Schedule entry

Schedule 6—New Entry

METHYLCHLOROISOTHIAZOLINONE in leave-on cosmetic products or therapeutic goods intended for leave-on topical application, **except** in preparations containing 0.0015 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total.

Appendix F, Part 3—New Entry

Poison	Warning statements	Safety direction
METHYLCHLOROISOTHIAZOLINONE	28	(over)(repeated) exposure may cause sensitisation

Implementation date: 1 June 2016.

Schedule 6—Amend Entry

METHYLCHLOROISOTHIAZOLINONE **except:**

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

b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total.

Implementation date: 1 October 2017.

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

2. New Chemical Entities – Medicines for human therapeutic use

2.1 Tofacitinib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of tofacitinib, a new chemical entity for a human therapeutic medicine.

Tofacitinib is a JAK1, 2 and 3 kinase inhibitor with some limited inhibitory activity against tyrosine kinase 2 (TyK2).

Tofacitinib is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Tofacitinib can be used alone or in combination with nonbiological DMARDs, including methotrexate.

Therapy with tofacitinib should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

The delegate decided to make a delegate-only decision in including tofacitinib to Schedule 4. The Advisory Committee on Medicines Scheduling (ACMS) was not consulted.

Scheduling status

Tofacitinib is not specifically scheduled and is not captured by any entry in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Tofacitinib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include tofacitinib in Schedule 4, with an implementation date of 1 February 2016.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purposes and the extent of use; (c) the toxicity of; and (e) the potential for abuse of tofacitinib.

The delegate decided that the reasons for the final decision comprise of the following.

- Tofacitinib is a new chemical entity with no clinical experience in Australia.

- The risks and benefits of the medicine have been considered and are outlined in the Product Information, Delegate's Request for ACPM advice and the TGA evaluation reports.
- The indication is for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Tofacitinib can be used alone or in combination with nonbiological DMARDs, including methotrexate. Therapy with tofacitinib should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.
- Experience of its use is limited in Australia.
- It is proposed for use in the community.
- The drug has specific toxicities related to its immunosuppressive effect (infection, malignancy) and other concerns which are discussed in the Product Information. It has been placed in Pregnancy Category D as preclinical studies indicated teratogenic effects and there is limited experience in pregnant women.
- The medicine has risks that require medical intervention, evaluation and monitoring by a medical practitioner.
- Treatment with tofacitinib should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.
- Labelling needs to comply with the requirements for a prescription only medicine. Medicine is packed as 5 mg film-coated tablets in blisters and bottles.
- It does not appear to produce dependency and the abuse potential appears to be low.

Schedule entry

Schedule 4—New Entry

TOFACITINIB.