Isothiazolinones: Human health tier III assessment

Chemical Name on the Inventory	CAS Number
3-Isothiazolone, 2-methyl-	2682-20-4
3(2H)-Isothiazolone, 5-chloro-2-methyl-	26172-55-4
3(2H)-Isothiazolone, 5-chloro-2-methyl-, hydrochloride	26530-03-0
3(2H)-Isothiazolone, 2-methyl-, hydrochloride	26172-54-3
1,2-Benzisothiazol-3(2H)-one	2634-33-5
1,2-Benzisothiazol-3(2H)-one, sodium salt	58249-25-5
1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine	38521-29-8
3(2H)-Isothiazolone, 4,5-dichloro-2-octyl-	64359-81-5
3(2H)-Isothiazolone, 2-octyl-	26530-20-1

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

For more detail on this program please visit: www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Synopsis

Various cosmetic and domestic products contain isothiazolinones as biocides or preservatives. Around the world, reports of skin sensitisation to isothiazolinones have increased over the years. The respective Tier II Human Health IMAP assessments for the isothiazolinones recommended a Tier III Human Health IMAP assessment to further characterise the risks from use of these products (NICNASa; NICNASb; NICNASc; NICNASd; NICNASe; NICNASf; NICNASg).

A detailed assessment of the exposure and risk, relating to skin sensitisation, was conducted to determine the appropriate hazard classification and use restrictions for each isothiazolinone. Based on the overall data, amendments to the current Hazardous Chemical Information System (HCIS) (Safe Work Australia) skin sensitisation classification with specific concentration limits for each isothiazolinone are recommended to protect workers. Amendments to the scheduling exemptions of isothiazolinones in Schedule 6 of

the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (SUSMP, 2019) and inclusion of isothiazolinones in Appendix F of the Poisons Standard are recommended.

Rationale for Tier III Assessment

There is international concern regarding the rise in rate of skin sensitisation to certain isothiazolinones. Isothiazolinones are used as biocides or preservatives in a wide range of consumer products including cosmetic, domestic and paint products. Currently, in Australia, only some of the isothiazolinones are Scheduled (listed with restrictions on use) in the Poisons Standard (SUSMP, 2019) and the exemptions are not consistent for those that are Scheduled. Due to the risk of skin sensitisation to consumers from using cosmetic, domestic and/or paint products containing isothiazolinones, a Tier III Human Health IMAP assessment was recommended in the respective Tier II Human Health IMAP assessments (NICNASa; NICNASb; NICNASc; NICNASd; NICNASe; NICNASf; NICNASg). The purpose of the Tier III Human Health IMAP assessment for each chemical are as follows:

- For BIT and its salts, and OIT, to assess in more detail the exposure and risk of skin sensitisation to these chemicals in cosmetic, domestic and paint products;
- For all the other isothiazolinones in this assessment, to further assess the exposure and risk of skin sensitisation to these chemicals in domestic and paint products;
- For all the isothiazolinones in this assessment, to determine whether the current HCIS (Safe Work Australia) skin sensitisation classification for each isothiazolinone should be amended for Work Health and Safety;
- For 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine, to evaluate the HCIS skin sensitisation classification;
- For BIT and its salts, to recommend whether they should be Scheduled on the Poisons Standard; and
- For all the isothiazolinones in this assessment, to determine whether concentration limits on the Poisons Standard should be consistent.

Chemical Identity

Chemical name on the Inventory and Synonyms	CAS Number
3-Isothiazolone, 2-methyl- MI MIT 2-methyl-3-isothiazolone methylisothiazolinone N-methylisothiazolin-3-one	2682-20-4

Chemical name on the Inventory and Synonyms	CAS Number
3(2H)-Isothiazolone, 5-chloro-2-methyl- MCI CMI CMIT 5-chloro-2-methyl-3-isothiazolone methylchloroisothiazolinone isothiazolinone chloromethyl	26172-55-4
3(2H)-Isothiazolone, 5-chloro-2-methyl-, hydrochloride 5-chloro-2-methyl-4-isothiazolin-3-one hydrochloride 5-chloro-2-methylisothiazolin-3-one hydrochloride 3(2H)-isothiazolone, 5-chloro-2-methyl-, hydrochloride (1:1) 5-chloro-2-methylisothiazol-3(2H)-one hydrochloride	26530-03-0
3(2H)-Isothiazolone, 2-methyl-, hydrochloride 2-methyl-4-isothiazolin-3-one, hydrochloride methylisothiazolinone hydrochloride	26172-54-3
1,2-Benzisothiazol-3(2H)-one BIT 1,2-benzisothiazol-3(2H)-one 1,2-benzisothiazolin-3-one 1,2-benzisothiazolone benzisothiazolinone	2634-33-5

Chemical name on the Inventory and Synonyms	CAS Number
1,2-Benzisothiazol-3(2H)-one, sodium salt sodium benzisothiazolinone	58249-25-5
1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine 1,2-benzisothiazol-3(2H)-one, compd. with ethane-1,2-diamine	38521-29-8
3(2H)-Isothiazolone, 4,5-dichloro-2-octyl- DCOIT dichloro-2-n-octyl-4-isothiazolin-3-one 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one	64359-81-5
3(2H)-Isothiazolone, 2-octyl- OIT octhilinone octylisothiazolinone 2-octyl-3(2H)-isothiazolone 2-octyl-4-isothiazolin-3-one	26530-20-1

Import, Manufacture and Use

Isothiazolinones are reported to be used as a preservative in cosmetic and domestic products (including paints) internationally. Available information on the types of products containing these chemicals, available to consumers in Australia and overseas, is provided in Table A1 in Appendix 1. While some of this information has been made available to NICNAS subsequent to publication of the original Tier II Human Health IMAP assessments for these chemicals, the majority of the information has been obtained from online searches, reports and databases (further details on the types of products, concentrations levels and sources of use information, is provided in Table A1 in Appendix 1).

For information on other reported categories of use for these chemicals, please refer to the respective Tier II Human Health IMAP assessments (NICNASa; NICNASb; NICNASc; NICNASd; NICNASe; NICNASf; NICNASg).

Cosmetic Use

The Cosmetic Ingredient Review (CIR) (2019) analysed the United States Food and Drug Authority (US FDA) voluntary cosmetic registration program database and the Personal Care Products Council's use concentration data. In 2019, the total number of uses of

MI has increased in to 6037, and MCI to 5137, since 1986. The highest reported use concentration of MCI/MI (3:1) was 7.5 ppm in leave-on products and 15 ppm in rinse-off products (CIR, 2019).

In comparison with the availability of information on the other isothiazolinones, minimal data are available on the concentrations of BIT and OIT in cosmetics. The chemicals have reported cosmetic uses as antibacterial agents. BIT was reported as being present in hand wash at a concentration of <1 % (refer to Table A1 in Appendix 1).

In Europe, isothiazolinones are also reported to be used as preservatives in tattoo and permanent make-up (PMU) inks (Hauri, 2014; Piccinini et al., 2015). In Dutch and Swiss studies, 229 tattoo and PMU inks were sampled. BIT, MI and MCI were detected in 24 %, 8 % and 2 % of samples, respectively. OIT was not found in any of the samples; it was reported that the studios had stopped purchasing OIT. In the samples containing BIT, the median measured concentration was 105 mg/kg (range: 30–424 mg/kg).

Paints

The concentrations of BIT, MI, MCI/MI, DCOIT and OIT in various paint products available in Australia were provided by the paint industry. Use concentrations ranged from 0.00002–0.12 % (refer to Table A1 in Appendix 1). Limited data were available for DCOIT in industrial paints, with use at a concentration of 0.2 % reported internationally (Friis et al., 2014).

In the US Household Products Database, paint products contained 1 or 2 isothiazolinones. High-performance liquid chromatography (HPLC) analysis of paints in Europe have revealed concentrations of BIT, MI and MCI up to 360, 300 and 14 ppm, respectively (Lundov et al., 2014). Another study has analysed 4 water-based wall paints sold in Belgium by HPLC to determine the concentration of isothiazolinones. MI was found in all 4 paints either with BIT (in 3 out of 4 paints) or on its own (Aerts et al., 2015) (refer to Table A1 in Appendix 1).

Domestic Products (other than Paints)

Australian uses in the marine industry for BIT that were reported under previous mandatory and/or voluntary calls for information include glaze, polish and gel coat products.

Australian uses for MI and MCI that were reported under previous mandatory and/or voluntary calls for information include marine and automotive aftermarket products, for example, waxes, rubbing compounds, polishes, cleaning products and sealants.

Highlighting pens have been identified through publicly available safety datasheets to contain <0.1 % MCI/MI mixture, BIT or OIT.

In the US Household Products Database (HPD), domestic products reported to contain ≤1 % BIT include laundry detergent, dishwashing liquid, floor cleaner, wood cleaner, glass cleaner, and disinfectant (refer to Table A1 in Appendix 1).

Biocidal products are reported to contain up to 190 g/kg (BIT) as registered in the Irish Department of Agriculture, Fisheries and Food's Biocidal Products Register (refer to Table A1 in Appendix 1).

Restrictions and Existing Work Health and Safety Controls

The current Australian and international restrictions on the use of isothiazolinones in cosmetic and paint products are compared in Table 1.

Table 1. Comparison of current restrictions on the use of isothiazolinones in consumer products, in addition to product categories identified as available to consumers in Australia (AUS) and internationally (INT).

Chemical and CAS #	Identified Consumer Uses	Cosmetic Restrictions		Paint Restrictions		Current HCIS classification for skin sensitisation	GPMT or LLNA studies lowest concentration	HRIPT studies Subjects sensitised at lowest concentrat
		AUS*	INT	AUS*	INT			

MI 2682-20-4	C (AUS; INT) D (AUS; INT) P (AUS; INT)	Schedule 6 restrictions apply, except in rinse-off cosmetic preparations containing ≤0.0015 % of MI.	EU - MI has a maximum authorised mixture concentration of 0.0015 %≠. Canada - MI is currently permitted at levels ≤0.0015 % in rinse-off products and NOT permitted in leave-on products (Health Canada, 2019). USA - CIR recommended a concentration of 100 ppm for rinse-off cosmetic products (CIR, 2019).	Schedule 6 restrictions apply, except in preparations that are not intended for direct application to the skin containing ≤0.1 % of MI.	EU^– Application for approval of use of MI as a preservative for products during storage is still in progress; this may include paint products (ECHA, 2019). The mixture of MCI/MI (3:1) is approved for use in DIY paint products with a concentration limit of 0.0015% (Biocidal Products Committee, 2015).	Category 1	LLNA 1.35 % MI (RAC, 2016a)	HRIPT 1/116 subjects sensitised at 0.04 % (20 μg/cm^2) MIT (RAC, 2016a)
MCI 26172-55-4	C (AUS; INT) D (AUS; INT)	Schedule 6 restrictions apply, except in rinse off cosmetic preparati	EU - a 3:1 mixture of MCI and MI has a maximum	Schedule 6 restrictions apply, except in preparations that are not	EU^– Application for approval of use of MCI as a preservative for	Category 1	LLNA (OECD 429) <0.003 % MCI/MI mixture	HRIPT 1/284 subjects sensitised at 0.00125 % MCI

	P (AUS; INT)	ons ≤0.0015 % of MCI and MI in total.	authorised mixture concentration of 0.0015 %≠. Canada - MCI/MI is currently permitted at levels ≤0.0015 % in rinse-off products and NOT permitted in leave-on products (Health Canada, 2019). USA - 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, 2019).	intended for direct application to the skin containing ≤0.1 % of MCI and MI in total.	products during storage is still in progress; this may include paint products (ECHA, 2019). See EU restriction description above for the mixture of MCI/MI (3:1).		(RAC, 2016b)	(Basketter et al., 1999)
BIT	C (INT)	Not in the	EU – BIT is not	None	EU^– Applicati	Category 1	GPMT (OECD	HRIPT

2634-33-5	D (AUS; INT) P (AUS; INT)	Poisons Standard	authorised for use in cosmetics as a preservative (CosIng).		on for approval of use of BIT as a preservative for products during storage is still in progress; this may include paint products (ECHA, 2019).	*Note: The Human Health Tier II IMAP assessment recommended Category 1B subclassification.*	406) 0.1 % BIT (induction) (SCCS, 2012)	5/58 subjects sensitised at 0.0725 % BIT (Basketter et al., 1999)
OIT 26530-20-1	C (INT) D (AUS; INT) P (AUS; INT)	Schedule 6 restrictions apply – no exemptions for cosmetic use *Note: Cosmetic use was not taken into consideration as part of this scheduling decision (TGA, 2008).*	EU – OIT is not authorised for use in cosmetics as a preservative (CosIng).	Schedule 6 restrictions apply, except in paints, jointing compounds and sealants containing ≤1 % of OIT (octhilinone) calculated on the non-volatile content. *Note: This chemical was scheduled in 1977 based on its use as a cotton seed fungicide*	Canada – Pest Management Regulatory Agency cancelled the use of OIT (octhilinone) as a preservative in paints and stains (Health Canada, 2017). EU^– Application for approval of use of OIT as a preservative for products during storage is still in	Category 1 *Note: The Human Health Tier II IMAP assessment recommended Category 1A subclassification.*	LLNA (OECD 429) 0.5 % OIT (RAC, 2018b)	HRIPT 1/222 subjects sensitised at 0.01 % OIT (RAC, 2018b)

				. The listing was subsequently amended to include the exemptions based on limited toxicological data (TGA, 2008).	progress; this may include paint products (ECHA, 2019).			
DCOIT 64359-81-5	P (AUS; INT)	Schedule 6 restrictions apply – no exemption for cosmetic use *Note: Cosmetic use was not taken into consideration as part of this scheduling decision (TGA, 2016).*	EU – DCOIT is not a permitted cosmetic ingredient (CosIng).	Schedule 6 restrictions apply – no exemptions. *Note: A proposal to include a concentration cut-off exemption for certain paint products was rejected by the scheduling delegate, with particular consideration to the fact that "animal*	EU^– Application for approval of use of DCOIT as a film preservative is still in progress (ECHA, 2019).	None *Note: The Human Health Tier II IMAP assessment recommended Category 1A subclassification.*	LLNA (OECD 429) 0.03 % DCOIT (RAC, 2018a)	HRIPT 4/34 subjects sensitised at 0.025 % DCOIT (RAC, 2018a)

				studies suggest skin sensitisation is possible at very low concentrations and therefore the substance, at all concentrations, continues to meet the criteria for Schedule 6" (TGA, 2016).			
3(2H)-Isothiazolone, 2-methyl-, hydrochloride 26172-54-3	D (INT) P (AUS; INT)	As per the Schedule entry for MI (see above restrictions)	No data available.	As per the Schedule entry for MI (see above restrictions)	No data available.	None *Note: The Human Health Tier II IMAP assessment recommended Category 1 classification.*	Skin sensitisation data for MI and MCI can be used as read-across for these chemicals.
3(2H)-Isothiazolone, 5-chloro-2-methyl-, hydrochloride	P (AUS; INT)	As per the Schedule entry for MCI (see above	No data available.	As per the Schedule entry for MCI (see above	No data available.	Category 1	

26530-03-0		restrictions)	restrictions)		
1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine 38521-29-8	No data available.	Not in the Poisons Standard	No data available.	None	Limited data available for this BIT salt. Skin sensitisation data for BIT and 1,2-ethanediamine (CAS No. 107-15-3) can be used as read-across (see **Health Hazard Information** section below).
1,2-Benzisothiazol-3(2H)-one, sodium salt (BIT sodium salt) 58249-25-5	No data available.	Not in the Poisons Standard	No data available.	None *Note: The Human Health Tier II IMAP assessment recommended Category 1B subclassification.*	Skin sensitisation data for BIT can be used as read-across

*AUS restrictions – Poisons Standard (SUSMP, 2019).

≠ Annex V (List of preservatives allowed in cosmetic products) to Regulation No. 1223/2009 on cosmetic products.

^ EU – Paint products shall only contain preservatives that are authorised under Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products.

C = Cosmetic; D = Domestic; P = Paint products; CIR = Cosmetic Ingredient Review; CosIng = European Commission Cosmetic Ingredients and Substances database; ECHA = European Chemicals Agency; GPMT = guinea pig maximisation test; HRIPT = human repeated insult patch test; LLNA = local lymph node assay; RAC = Committee for Risk Assessment; SCCS = Scientific Committee on Consumer Safety; TGA = Therapeutic Goods Administration.

Australia

Hazard Classification

Table 1 shows the existing skin sensitisation categories in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). For BIT, BIT sodium salt, OIT and DCOIT, the respective Tier II Human Health IMAP assessments recommended HCIS sub-classification for skin sensitisation, while for MI, MCI and 3(2H)-isothiazolone, 5-chloro-2-methyl-, hydrochloride, the recommended skin sensitisation classification was Category 1 (refer to Table 1) (NICNASa; NICNASb; NICNASc; NICNASd; NICNASe; NICNASf; NICNASg).

Poisons Standard

Despite the similar consumer use patterns and toxicological concerns, there is notable variability in the current scheduling restrictions across the isothiazolinones; a comparison is presented in Table 1.

As detailed in the Tier II assessments, most of the isothiazolinones are currently listed in Schedule 6 (S6) of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (SUSMP, 2019). Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with **'Poison'** (SUSMP, 2019).

A Schedule entry includes all salts and derivatives of the poison unless it specifically states otherwise (SUSMP, 2019). Therefore, for the isothiazolinones that are scheduled, this also includes their respective salts.

MCI and MI are also listed in Appendix F of the Poisons Standard, which requires products containing MI or MCI, at any concentration level, to be labelled with the warning statement '(Over) (Repeated) exposure may cause sensitisation' (SUSMP, 2019).

OIT (as octhilinone) is listed in Appendix E of the Poisons Standard, which requires products containing containing OIT, at any concentration, to be labelled with appropriate first aid statements in accordance with Appendix E (SUSMP, 2019).

DCOIT does not have any associated Appendix E or F requirements (SUSMP, 2019).

In addition to specific requirements under the Poisons Standard, the mandatory standard for ingredient labelling on cosmetic products (*Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991*) requires the listing of all cosmetic ingredients on the product and/or container (Trade Practices, 2008).

International

While international restrictions on use exist for several of the isothiazolinones (NICNASa, NICNASb; Table 1), these restrictions have been recently reviewed by relevant authorities. In this section, updates to international restrictions on the use of isothiazolinones in consumer products are summarised, which have occurred subsequent to the publication of the NICNAS Tier II Human Health IMAP assessments of those chemicals.

Europe

MI, as well as the mixture of MCI and MI (in the ratio of 3:1) (CAS No. 55965-84-9) are listed on Annex V (*List of preservatives allowed in cosmetic products*) to Regulation No. 1223/2009 on cosmetic products, with a maximum concentration permitted in rinse-off products of 0.0015 %. BIT and OIT are not listed in Annex V (*List of preservatives allowed in cosmetic products*) to Regulation No. 1223/2009 on cosmetic products, and therefore, are not allowed in cosmetic products.

The Scientific Committee on Consumer Safety (SCCS) of the EU assessed the use of benzisothiazolinone (BIT) as a preservative in cosmetic products in 2012, and concluded that until safe levels of exposure have been established, the use of benzisothiazolinone in cosmetic products as a preservative or for other functions cannot be considered safe in relation to sensitisation (SCCS, 2012).

The 13th Adaptation to Technical Progress (ATP) to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation), amended the CLP Regulation to include updated requirements for MI and MCI in Annex VI to CLP Regulation. According to the CLP Regulation, mixtures containing either MI or the mixture of MCI/MI (ratio of 3:1) at concentrations ≥0.00015 % (equivalent to one-tenth of the specific concentration limit of 0.0015 % for the chemicals) are required to label packaging with the statement: *EUH208-'Contains (name of sensitising substance). May produce an allergic reaction'.*

In the EU, paint products shall only contain preservatives that are authorised under Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products. Preservatives must be approved for the specific product type (PT).

According to the European Chemicals Agency (ECHA, 2019) Biocidal Active Substances database, the mixture of MCI/MI (ratio of 3:1) is approved for use as a preservative for products during storage (PT06); this approval includes use in paints and coatings. Additionally, as a condition of approval for non-professional users, the end-use concentration of MCI/MI in the preserved product (paints and coatings, liquid detergents, adhesives and sealants and household products) must be reduced below the concentration limit of 0.0015 % (15 ppm), in order to take into account the sensitising properties of MCI/MI (Biocidal Product Committee (BPC), 2015)

No specific approvals exist for the use of MI or MCI, separately (i.e. not a mixture), as preservatives in paints; however, initial applications (PT06) for MI, MCI, OIT and BIT are is still in progress (see Table 1). It is unclear whether the applications include consideration of use in paint products, as no further information is available (ECHA, 2019).

The following isothiazolinones are approved for use as a preservative for product types other than paint products for domestic use:

- OIT: wood preservatives (PT08);
- DCOIT: wood preservatives (PT08) and anti-fouling products (PT21).
- MI: preservatives for liquid-cooling and processing systems (PT11), slimicides (PT12), and working and cutting-fluid preservatives (PT13) (ECHA, 2019).

Although not specifically a restriction, there is an incentive in the EU to limit use concentration of isothiazolinones for paints and varnishes in order to be awarded the EU Ecolabel. Paints and varnishes awarded the EU Ecolabel must meet the requirements set out in the Commission Decision (EU) (2014/312/EU: establishing the ecological criteria for the award of the EU Ecolabel for indoor and outdoor paints and varnishes, 28 May 2014). The award aims to encourage minimal use of hazardous substances in products, and promote products that are less hazardous to human and environmental health. According to the criteria for awarding the EU Ecolabel, the sum total of isothiazolinone compounds in any paint or varnish shall not exceed 0.05 % (500 ppm), with the exception of outdoor wood paints and varnishes which shall not exceed 0.20 %. BIT, MI, MCI/MI mixture and OIT are also subject to their contribution to the sum total of isothiazolinone compounds in the final ready to use product.

The Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have proposed to prohibit substances classified as skin sensitisers for use in tattoo and PMU inks (RAC and SEAC, 2019).

Canada

MI, as well as the combination of MCI and MI (MCI/MI), are listed on Health Canada's List of Ingredients that are Restricted for Use in Cosmetic Products (Cosmetic Ingredient Hotlist), with a maximum concentration of 0.0015 % in rinse-off products; neither MI or MCI/MI are permitted in leave-on products. Additionally, if MI is present in formulation with MI/MCI in combination, the cumulative total concentration of MI and MI/MCI may not exceed 0.0015 %. MCI is only permitted when present in combination with MI (Health Canada, 2019).

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the Pest Control Products Act, re-evaluated OIT as a material preservative. As an outcome of this re-evaluation, the PMRA has cancelled the use of OIT as a material preservative in coatings (paints and stains) to address potential risks of concern to human health (Health Canada, 2017). The PMRA also recommended a:

- reduction of the maximum application rate of OIT in building materials, aqueous emulsions and adhesives, and polymer compounds;
- prohibition of use of OIT in adhesives, polymer and vinyl compounds for food contact materials; and
- prohibition of use of OIT in polymer and vinyl compounds for children's toys.

USA

The Cosmetic Ingredient Review (CIR) Expert Panel reassessed the safety of methylisothiazolinone and methylchloroisothiazolinone (MCI/MI) as used in cosmetics, based on multiple reported incidences of sensitisation internationally since the original report was published in 1992. While an amended conclusion is yet to be finalised by the Panel, the draft amended report did include the following findings (CIR, 2019):

- Some leave-on cosmetic products still presented a skin sensitisation risk at the recommended safe concentration of 7.5 ppm.

- In most, but not all rinse-off products, 15 ppm MCI/MI was not associated with a potential increased risk of skin sensitisation induction.
- Individuals previously sensitised to MCI/MI should avoid products that contain this ingredient mixture, or either constituent.
- The data are insufficient to support the safety of MCI/MI in products which may be incidentally inhaled.

Exposure

Public Exposure

There is widespread exposure of the public to isothiazolinones through their use in various cosmetic and domestic products, based on studies discussed below.

In an aggregate exposure assessment based on a survey of the Swiss population's exposure to isothiazolinones in cosmetic and domestic products, aggregate exposure for different body parts to BIT and OIT was reported to be higher compared to that for MI and MCI (Table 2) (Garcia-Hidalgo et al., 2018). This is explained by higher concentrations of BIT and OIT measured in various types of household detergents, ranging from 3.8–186 ppm (BIT), and 7.9 ppm (OIT) (Garcia-Hidalgo et al., 2017). Aggregate exposure was defined as the sum of the exposures to the same isothiazolinone across different product categories. This model calculates exposure in the skin (as absorbed through the stratum corneum) at an individual level. The exposure estimates were expressed as amount absorbed per skin surface area (ng/cm^2) for different body locations and represent internal concentrations in the skin (Garcia-Hidalgo et al., 2018).

Table 2. 99th percentile aggregate exposure (Garcia-Hidalgo et al., 2018)

Body part	99th percentile Aggregate exposure (ng/cm^2)
BIT	
Arms	15.4
Palms	15.4
Back of hands	15.4
OIT	
Palms	1.28

Body part	99th percentile Aggregate exposure (ng/cm^2)
Back of hands	1.28
MI	
Palms	0.949
Back of hands	0.549
CMI	
Arms	0.0835
Palms	0.0835
Back of hands	0.0835

The highest domestic sources of BIT, OIT, MI and MCI contributing to the aggregate exposure were all-purpose cleaner (BIT), floor cleaning liquid and fungicide spray (OIT), dishwashing detergent (MI), and all-purpose cleaning liquid (MCI). Only 4 cosmetic product categories, such as shampoo, contributed to the aggregate exposure for MI and MCI (Garcia-Hidalgo et al., 2018).

Isothiazolinones are widely used in paints. MI and BIT were identified in over 90 % of paints used in Europe and the USA (Thomsen et al., 2018; Goodier et al., 2018). In addition to dermal exposure to isothiazolinones when applying paint, the public may also be exposed to the chemicals from their emissions from freshly painted walls. The emissions from gypsum board painted with in water-based paints containing MI, BIT, and MCI were measured in climate chambers and in an apartment. In the chamber experiment, emission of MI peaked within hours of application, but then continued at a slow rate for more than 42 days. MCI was emitted more slowly and peaked after several days. BIT emissions were all around the limit of detection. In the apartment, emission of MI was detected several days after application (Lundov et al., 2014). Five female patients were reported to develop airborne contact dermatitis to newly painted homes. The total concentration of MCI/MI in paint and varnish used at home was from 5–28.4 mg/kg as measured by HPLC. Air concentrations of MCI released from paint was initially 80 µg/m^3, and after 4 weeks, it was 5 µg/m^3 (Bohn et al., 2000).

Health Hazard Information

Skin sensitising potential of isothiazolinones at low concentrations

The isothiazolinones are considered to be skin sensitisers, as detailed in the respective Tier II Human Health IMAP assessments (NICNASa; NICNASb; NICNASc; NICNASd; NICNASe; NICNASf; NICNASg) and the additional data identified in this Tier III Human

Health IMAP assessment (refer to Tables A2-A5 in Appendix 2 for summaries).

The main concern in regards to these chemicals is the low concentrations at which elicitation of skin sensitisation reactions have been reported or observed, and the expectation that the sensitised individuals were induced at current use concentrations.

A number of case reports are available of individuals developing dermatitis or allergic symptoms after exposure to cosmetic and domestic products, or freshly painted homes, or occupationally in a paint manufacturing factory (refer to Table A3 in Appendix 2 for summaries). At the paint factory where 4 workers developed occupational contact dermatitis, products contained up to 10 % MI, 1 % MCI, 2.5 % BIT and/or 2.5 % OIT (Thyssen et al., 2006).

MI, MCI and their salts

While limited data are available for the salts of MI and MCI (CAS Nos. 26530-03-0; 26172-54-3), data for MI and MCI are considered to be suitable read-across for these salts. The additional human and animal data provided in this Tier III Human Health assessment warrant a sub-classification of Category 1A for MI, MCI and their salts (refer to **Recommendation: Work Health and Safety** section).

Retrospective studies have analysed a particular group of patient medical records collected from previous years. The retrospective studies summarised in this section include patients diagnosed with sensitisation to isothiazolinones through patch testing at dermatology centres indicate elicitation, due to previous exposure to various products containing the chemicals. The concentrations of MI and MCI/MI used in patch tests at different dermatology centres were 0.02–0.2 % and 0.01–0.02 %, respectively.

Several retrospective studies of patients diagnosed with dermatitis have reported high skin sensitisation rates to MI and/or MCI/MI in various countries (refer to Table A2 in Appendix 2 for summaries). An analysis of 8680 patients in Belgium from 2010–2013 revealed that the rate of sensitisation to MCI/MI increased from 3.6 % (2010) to 5.3 % (2013). Similarly, the rate of sensitisation to MI increased from 3.1 % (2010) to 7.2 % (2013) (Aerts et al., 2014). In North America from 2013–2014, the percentage of patients (n = 4860) sensitised to MI was 10.7 %, and to MCI/MI was 6.3 % (Zirwas et al., 2017).

The induction values for MI and MCI are below the cut-off of 2 % for sub-classification of Category 1A, according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS, 2009). Table 1 shows the lowest concentrations of the chemical to induce sensitisation in humans or give a stimulation index (SI) ≥3, as reported in the additional HRIPT and LLNA data (refer to Tables A4–A5 in Appendix 2 for summaries). HRIPT studies in subjects have used various concentrations of MI and MCI; the lowest concentrations to induce sensitisation to these chemicals were 0.04 % MI and 0.00124 % MCI (Basketter et al., 1999; RAC, 2016a and b). LLNA studies reported EC3 values (the effective concentration inducing a stimulation index of 3, i.e. a 3-fold increase in lymph node cell proliferation) of 1.35 % and 0.003 % for MI and MCI/MI, respectively (RAC, 2016a and b). Further, the dermatological data, which measure elicitation still give evidence of induction conditions for MI and MCI. This is because widespread exposure to these chemicals is at a maximum of 0.01 % MI and 0.0015 % MCI, indicating that the majority of these patients would have been induced at these concentrations.

BIT and its salts

The additional human and animal data provided in this Tier III Human Health IMAP assessment warrant a sub-classification of Category 1A for BIT and salts of BIT (refer to **Recommendation: Work Health and Safety** section).

Retrospective studies of large numbers of patients with diagnosed allergies indicate significantly high rates of positive patch test reactions to BIT. In these studies, BIT was not always included in patch tests at dermatology centres. Therefore, the number of people actually sensitised to BIT may be higher than what has been reported. The concentrations of BIT used in patch tests at different dermatology centres were 0.05 % and 0.1 %. In studies of patients with known allergies or contact dermatitis (Table A2 in Appendix 2):

- 7 out of 202 painters had a positive patch test reaction to 0.1 % BIT (Fischer et al., 1995);
- 4 out of 194 patients tested had a positive reaction to 0.05 % BIT only, and 8 to both BIT and OIT (Aerts et al., 2014);
- 3 out of 152 tested had a positive reaction to 0.1 % 1,2-benzisothiazolin-3-one, sodium salt (Geier et al., 2004).

Reliable data to establish the relevant induction concentrations are not available. Cross-sensitisation with MI or MCI cannot be ruled out as a cause of elicitation reactions (refer to **Cross-sensitisation studies** section).

The lowest concentration of BIT to elicit sensitisation reactions in 5 out of 58 subjects was 0.0725 % based on historic HRIPT studies. This result was complicated by the presence of 1,2-ethanediamine which is also a skin sensitiser (Basketter et al., 1999). In a GPMT conducted according to OECD 406, 9 out of 20 animals in the test group reacted positively to 0.1 % BIT intradermal induction

concentration, giving a response incidence of 45 % (SCCS, 2012). In a non-guideline LLNA study, the lowest concentration to give a ≥3-fold increase in test animals compared to vehicle-control group was 10 % BIT (Botham et al., 1991). It is noted that the SCCS reported an EC3 of 2.3 % for BIT; however, no LLNA experimental details were provided (SCCS, 2012).

One recommendation from the Tier II assessment of 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine was to evaluate, as part of an IMAP Tier III assessment, the sensitisation classification for the chemical (NICNASe). No specific data are available for 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine. Nevertheless, the available data for the parent chemicals, BIT and 1,2-ethanediamine (NICNASh), are applicable for determining the sensitisation potential, and hence, the classification of 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine.

In a non-guideline LLNA study, the reported EC3 for 1,2-ethanediamine (in acetone:olive oil) was ≥2.5 % (Kimber et al., 1998). Based on the available data, BIT appears to be a more potent skin sensitiser compared with 1,2-ethanediamine; therefore, the skin sensitisation potential of 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine is expected to be largely due to the potency of BIT.

The chemical, 1,2-Ethanediamine is also a respiratory sensitiser with the HCIS classification of Respiratory Sensitisation Category 1. It has a high vapour pressure and is a volatile chemical which produces vapour at room temperature and in atmospheric conditions, which facilitates inhalational exposure in humans. When 1,2-ethanediamine is present as a non-volatile salt in 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine, the potential for inhalational exposure and subsequent respiratory sensitisation would be present in products that are applied by spraying (e.g. spray paint).

OIT and DCOIT

The Human Health Tier II IMAP assessments' recommended sub-classification of Category 1A for OIT and DCOIT remain unchanged (NICNASf; NICNASg).

Retrospective analyses of patients with diagnosed allergies have identified a small percentage that are sensitised to OIT; however, patch testing for OIT at dermatology centres was not always performed; thus, the number of people actually sensitised to OIT may be higher than what has been reported. None of the retrospective analyses included DCOIT. The concentrations of OIT used in the patch tests at different dermatology centres were 0.025 % and 0.1 %. In studies of patients with known allergies or contact dermatitis (Table A2 in Appendix 2):

- 1 out of 202 painters reacted positively to 0.1 % OIT (Fischer et al., 1995);
- 2 out of 199 metalworkers had a positive patch test reaction to 0.025 % OIT (Geier et al., 2004);
- 23 out of 199 patients tested reacted to 0.1 % OIT only, and 8 to both BIT and OIT, as per BIT (Aerts et al., 2014).

Studies of HRIPT, with limited experimental details provided, for OIT and DCOIT indicate that the lowest concentrations to induce sensitisation were 0.01 % OIT and 0.025 % DCOIT (RAC, 2018a, b; Table A4 of the Appendix). Across the LLNA studies, the lowest concentrations to give SI ≥3 for OIT and DCOIT were 0.5 % and 0.03 %, respectively (Table A5 in Appendix 2).

Some case reports of workers in paint or textile factory developed various allergic symptoms following introduction of OIT or DCOIT into product manufacture (Table A3 in Appendix 2).

Cross-sensitisation studies

The similarity in the chemical structure of the isothiazolinones, in that they contain the isothiazolinone ring, suggest that there is a potential for cross-sensitisation. A study has investigated the similarity in sensitisation response of immune cells to MI, BIT and OIT in mice. CBA female mice (8/group) were exposed to 0, 0.13, 0.4 or 1.2 % MI (in acetone:olive oil, 4:1) for induction on the dorsal side of both ears and challenged with 0.4 % MI, 1.9 % BIT, or 0.7 % OIT. No significant differences in the T and B lymphocyte immune responses in the draining auricular lymph nodes were observed after challenge with MI, BIT or OIT, suggesting that cross-reaction between MI and BIT, or MI and OIT, is possible (Schwensen et al., 2017).

In a retrospective study of dermatitis patients allergic to MI and/or MCI/MI in Belgium, the likelihood of cross-sensitisation between MI and OIT in some patients that had positive reactions to OIT and MI/MCI cannot be ruled out (Aerts et al., 2014). It should also be noted that isothiazolinones are extensively used as biocides in various products to which people are exposed to making it difficult to ascertain the extent of cross-sensitisation.

Risk Characterisation

Critical Health Effects

For the purposes of this Tier III Human Health IMAP assessment, the critical health effect for risk characterisation is skin sensitisation. Other critical health effects, as identified in the Tier II Human Health IMAP assessments for these chemicals, remain unchanged.

Although the HRIPT and animal studies have shown variable results for the lowest concentrations to induce sensitisation, the problem remains that much of the population has already been exposed to products containing isothiazolinones. While the main concern would be eliciting sensitisation in previously sensitised individuals, the concentrations at which sensitisation is elicited are much lower than that for induction. The concentrations at which sensitisation are elicited for each isothiazolinone cannot be identified based on the available data.

There are some data that indicate the potential for cross-sensitisation between the isothiazolinones (refer to **Cross-sensitisation studies** section).

Public Risk Characterisation

A large amount of data show that a significant number of individuals are sensitised, not only to MI and MCI/MI, but also to BIT and OIT. Public exposure to these chemicals are mainly from domestic products that are used frequently by the population. Cosmetic use also contributes significant exposure to MI and MCI, although recent scheduling changes in Australia will limit this exposure. Cases of individuals developing allergic reactions to newly painted rooms have also been reported.

Cosmetic Use

MI and MCI and their salts

The use of the chemicals are restricted both internationally and in Australia (refer to **Restrictions and Existing Work Health and Safety Controls** section). In Australia, MI and MCI (including their salts) are listed in Schedule 6 of the Poisons Standard (SUSMP, 2019). This effectively restricts the use of these chemicals in cosmetic products with exemptions for rinse-off cosmetics at low concentrations (≤0.0015 % (15 ppm) MCI and MI in total). An international evaluation recently proposed that for most rinse-off products, 15 ppm MCI/MI was not associated with a potential increased risk of skin sensitisation induction (CIR, 2019). Therefore, the current Poisons Standard restriction for use in rinse-off cosmetics is considered adequate to minimise the risk the public from use of the chemicals in cosmetics (refer to **Recommendation** section).

Other isothiazolinones

OIT and DCOIT are currently listed in Schedule 6 of the Poisons Standard (SUSMP, 2019). This effectively prohibits the use of these chemicals in cosmetic products.

The use of BIT in cosmetic products has been identified overseas. Positive patch test results for BIT have been observed at 0.05–0.1 % (refer to **Health Hazard Information: BIT and its salts** section). In the EU, BIT is not allowed as a preservative in cosmetic products (refer to **Restrictions and Existing Work Health and Safety Controls** section). In Australia, BIT should not be permitted to be used in cosmetic products, similar to the EU restriction. Inclusion of BIT in Schedule 6 in the Poisons Standard is warranted (refer to **Recommendation** section).

Given widespread exposure to isothiazolinones and the potential for cross-sensitisation, there is insufficient data to determine the levels that induce or elicit sensitisation in humans for each chemical. In the absence of any regulatory controls, the characterised critical health effect of skin sensitisation has the potential to pose an unreasonable risk under the identified uses.

Use in tattoo and permanent make up (PMU)

The chemicals have identified use in tattoo and PMU inks with BIT being the most prevalent chemical. There is insufficient data to determine whether induction or elicitation of sensitisation from use of the chemicals in tattoo inks is an issue. In Europe, there is a proposal to prohibit all classified skin sensitisers from use in tattoo inks (refer to **Restrictions and Existing Work Health and Safety Controls: International** section).

Tattoo and PMU inks containing MI, MCI, OIT and DCOIT have labelling requirements due to the chemicals being listed in the Poisons Standard. However, there are no requirements for the isothiazolinones to be listed by name as ingredients in tattoo inks. Therefore, consumers who are already (cross-)sensitised to certain substances are unaware of whether these chemicals are present in tattoo inks. Full ingredient disclosure on product labels would enable consumers to identify ingredients that may be of concern to them and take precautions accordingly (refer to **Recommendation** section).

Paints

Isothiazolinones are used in paint products as preservatives. Some paint products contain 1 or 2 isothiazolinones. Direct exposure to paint formulations containing isothiazolinones have resulted in allergic reactions. Cross-sensitisation between the isothiazolinones cannot be ruled out. In addition, cases of individuals developing allergic reactions to newly painted rooms have also been reported.

Paint products containing MI, MCI, OIT and DCOIT have labelling requirements due to the chemicals being listed in the Poisons Standard. However, there are different exemptions for these chemicals in the Poisons Standard (refer to **Restrictions and Existing Work Health and Safety Controls** section). There are no restrictions on the use of BIT in domestic products.

In 2016, the Advisory Committee on Chemicals Scheduling (ACCS) reviewed the available skin sensitisation data on DCOIT in regards to paint. The ACCS determined that there was insufficient evidence to support a proposed concentration cut-off for exemption from scheduling in the Poisons Standard (TGA, 2016). The Committee advised that “skin exposure during the use of the paint is highly likely in the domestic setting with a significant risk of skin sensitisation necessitating label warnings and the substance retention in Schedule 6”, and also that “animal studies suggest skin sensitisation is possible at very low concentrations and; therefore, the substance at all concentrations, continues to meet the criteria for Schedule 6” (TGA, 2016).

The reasoning and advice provided by the ACCS in Australia for the use of DCOIT in paints is considered relevant to the other isothiazolinones, as the available data indicate the potential for skin sensitisation at very low concentrations for these chemicals.

Currently, there are no requirements for the isothiazolinones to be listed by name as ingredients in paint products. Full ingredient disclosure on paint product labels would enable consumers to take precautions when using these products. Based on the available information, it is recommended that the isothiazolinones be included in Schedules with similar exemptions for paint products (refer to **Recommendation** section).

Domestic Products (other than Paints)

Isothiazolinones are widely used in other domestic products not mentioned above (refer to **Public Exposure** section).

Although the risk from the use of isothiazolinones in domestic products (other than paint) appear lower than for other uses, the potential for elicitation of sensitisation from use of products containing the chemicals cannot be ruled out. Domestic products containing MI, MCI, OIT and DCOIT have labelling requirements due to the chemicals being Scheduled in the Poison Standard. There are different exemptions for this labelling for these chemicals. There are no restrictions for the use of BIT in domestic products. A similar labelling requirement for domestic products, as indicated above, would allow consumers to take precautions when using these products.

Occupational Risk Characterisation

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

Among painters the isothiazolinones MCI/MI, MI alone, OIT, and BIT are some of the most common reasons for occupational contact dermatitis (refer to Appendix A2-A3 in Appendix 2). In a Danish study investigating occupational contact dermatitis in painters, a high percentage of painters registered in the National Database for Contact Allergy tested positive to MI (27 %), OIT (25 %), MCI:MI (22 %) and BIT (19 %) (Mose et al., 2012).

Given the critical health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise all routes of exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The available data support amendment of the skin sensitisation classification for the chemicals in this assessment (see **Recommendation** section).

NICNAS Recommendation

Based on the available information in this Tier III Human Health IMAP assessment further risk management is required.

It is likely that elicitation concentrations would be below those at which the preservatives would be effective. However, the size of the induced population could be reduced over time by implementation of controls intended to minimise or prevent induction.

It is recommended that risks to public health and safety from the potential use of isothiazolinones be managed through changes to Poisons Standard scheduling, and risks for workplace health and safety be managed through changes to HCIS classification and labelling.

Regulatory Control

Public Health

Currently, there are inconsistencies in the schedule entries in the Poisons Standard for the chemicals in this assessment.

While the current scheduling entries in the Poisons Standard for MI and MCI regarding rinse-off cosmetic use are considered appropriate, the use of these chemicals in paints, other domestic products and tattoo inks does not appear to have been taken into consideration as part of that scheduling proposal. Concerns regarding use in paint and tattoos arose as a consequence.

There are currently no restrictions for BIT in the Poisons Standard (SUSMP, 2019). An entry is recommended for ISOTHIAZOLINONES not specified elsewhere in the Schedules be included in Schedule 6 in the Poisons Standard, to replace the existing OIT (octhilinone) and DCOIT schedule entries. In conjunction with this combined scheduling entry for ISOTHIAZOLINONES, it is also recommended that BIT, OIT and DCOIT be included in the index of the Poisons Standard, each with a cross reference to ISOTHIAZOLINONES. A new warning statement in Appendix F is recommended.

Table 3 shows the recommended Poisons Standard entries for the isothiazolinones.

Table 3. Recommended Poisons Standard entries

Chemical and CAS #	Recommended Schedule 6 exemption	Recommended Appendix F warning statement

Chemical and CAS #	Recommended Schedule 6 exemption	Recommended Appendix F warning statement
MI 2682-20-4	**except:** ● in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.0015 per cent or less of methylisothiazolinone; or ● in other preparations that are not intended for direct application to the skin containing 0.05 per cent or less of isothiazolinones in total when labelled with the statements: CONTAINS ISOTHIAZOLINONES REPEATED EXPOSURE MAY CAUSE SENSITISATION (written in letters not less than 1.5 mm in height)	NEW Statement: CONTAINS ISOTHIAZOLINONES REPEATED EXPOSURE MAY CAUSE SENSITISATION (written in letters not less than 1.5 mm in height)

Chemical and CAS #	Recommended Schedule 6 exemption	Recommended Appendix F warning statement
MCI 26172-55-4	**except:** ● 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 ● in other preparations that are not intended for direct application to the skin containing 0.05 per cent or less of isothiazolinones in total when labelled with the statements: CONTAINS ISOTHIAZOLINONES REPEATED EXPOSURE MAY CAUSE SENSITISATION (written in letters not less than 1.5 mm in height)	
BIT 2634-33-5 OIT 26530-20-1 DCOIT 64359-81-5	ISOTHIAZOLINONES not elsewhere specified in these Schedules, **except** in preparations that are not intended for direct application to the skin containing 0.05 per cent or less of isothiazolinones in total and labelled with the statements: CONTAINS ISOTHIAZOLINONES REPEATED EXPOSURE MAY CAUSE SENSITISATION (written in letters not less than 1.5 mm in height)	

Note: Appendix F warning statements apply to substances and their preparations at all concentrations, unless specified in the Appendix F listing.

Work Health and Safety

The chemicals are recommended for classification and labelling for skin sensitisation aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as listed in Table 4. The recommended classifications for other endpoints are included in the Human Health Tier II IMAP assessments for these chemicals.

The generic concentration limit for the relevant classification (0.1 % for skin sensitisation category 1A and 1 % for skin sensitisation category 1B) are not considered appropriate to protect workers, in particular painters.

In Europe, the amended the CLP Regulations (13th ATP) include the following specific concentration limits (SCL) for skin sensitisation – Category 1:

- MI—0.0015 %
- MCI:MI (3:1) —0.0015 %
- BIT—0.05 %
- OIT—0.05 %.

SCLs can be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the generic classification limit. SCLs for skin sensitisation are generally applied for the most potent skin sensitisers classified in 1A. They are typically set based on potency using results from animal testing. Based on results from LLNA and GPMT studies, MCI and DCOIT are considered extreme sensitisers and MI, BIT and OIT are considered strong sensitisers (ECHA, 2017; refer to Table A5 in Appendix 2). However, based on the prevalence of human patch test positive results for MI when the evidence is that induction followed exposure at 0.01 % (refer to Table A4 in Appendix 2), it is considered appropriate to treat MI as an extreme sensitiser.

Taking into account the potency of sensitisation in animal studies, and the prevalence of contact allergy (see **Health Hazard Information** section), the SCLs set in Europe are considered appropriate to help protect workers against the risk of sensitisation. An SCL of 0.0015 % should also be applied for DCOIT. Products containing chemicals above the SCLs would:

- be classified as skin sensitisers
- disclose the identity of the chemical on the label and safety data sheet.

An amendment to the current HCIS classification for skin sensitisation is recommended for MI, MCI and their salts, and for BIT and its salts (Table 4).

For OIT and DCOIT, the Tier II Human Health IMAP assessment recommended sub-classifications remain unchanged.

Table 4. Existing and recommended HCIS classification

Chemical and CAS #	Current GHS classification (HCIS) for skin sensitisation	Recommended GHS classification (HCIS) for skin sensitisation
MI 2682-20-4	May cause an allergic skin reaction - Category 1 (H317)	May cause an allergic skin reaction - Category 1A (H317): C ≥0.0015 %
MCI 26172-55-4	May cause an allergic skin reaction - Category 1 (H317)	May cause an allergic skin reaction - Category 1A (H317): C ≥0.0015 %

Chemical and CAS #	Current GHS classification (HCIS) for skin sensitisation	Recommended GHS classification (HCIS) for skin sensitisation
3(2H)-Isothiazolone, 2-methyl-, hydrochloride 26172-54-3	None *Note: The Human Health Tier II IMAP assessment recommended Category 1 classification.*	May cause an allergic skin reaction - Category 1A (H317): C ≥0.0015 %
3(2H)-Isothiazolone, 5-chloro-2-methyl-, hydrochloride 26530-03-0	May cause an allergic skin reaction - Category 1 (H317)	May cause an allergic skin reaction - Category 1A (H317): C ≥0.0015 %
BIT 2634-33-5	May cause an allergic skin reaction - Category 1 (H317) *Note: The Human Health Tier II IMAP assessment recommended Category 1B subclassification.*	May cause an allergic skin reaction - Category 1A (H317): C ≥0.05 %
1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine 38521-29-8	None	May cause an allergic skin reaction - Category 1A (H317): C ≥0.05 %
1,2-Benzisothiazol-3(2H)-one, sodium salt 58249-25-5	None *Note: The Human Health Tier II IMAP assessment recommended Category 1B subclassification.*	May cause an allergic skin reaction - Category 1A (H317): C ≥0.05 %
OIT 26530-20-1	May cause an allergic skin reaction - Category 1 (H317) *Note: The Human Health Tier II IMAP assessment recommended Category 1A subclassification.*	May cause an allergic skin reaction - Category 1A (H317): C ≥0.05 %

Chemical and CAS #	Current GHS classification (HCIS) for skin sensitisation	Recommended GHS classification (HCIS) for skin sensitisation
DCOIT 64359-81-5	None *Note: The Human Health Tier II IMAP assessment recommended Category 1A subclassification.*	May cause an allergic skin reaction - Category 1A (H317): C ≥0.0015 %

Advice for consumers

Products containing the chemical should be used according to instructions on the label.

Advice for industry

The advice provided in the Tier II Human Health IMAP report remains unchanged.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

Appendix 1

Table A1. Concentrations of some isothiazolinones in cosmetic and domestic products, including paint.

	Chemical name					
	BIT	**MI**	**MCI**	**MCI/MI**	**DCOIT**	**OIT**
CAS No.	2634-33-5	2682-20-4	26172-55-4	55965-84-9	64359-81-5	26530-20-1
Product type	The Irish Department of Agriculture, Fisheries and Food Biocidal Products Register (content (g/kg))					
Biocide	11–190	11–25	115.5	0.17–139	45	9–158
Dishwashing liquid	0.3		0.014	0.014		
Marine antifouling					9.7–24.9	

Wood protector				30		
Carpet cleaner				2		
Cleaning gel	0.05	0.05				
	The Danish Ministry of the Environment's Survey of Biocidal Products in Denmark (typical dose levels (% of active agent))					
Biocide	0.01–0.4	0.1–0.4		0.005–0.3		0.1–3.0
Paint preservative				0.005–0.4		0.1–2.0
Plastic	0.1–3					
	Maximum concentration (%) in products in Denmark (Friis et al., 2014)					
Paints and varnishes	0.05* (144)	0.024* (110)	0.001 (75)	0.022 (105)	0.2 (38)	0.1 (60)
	Concentration (%) in products in the US HPD					
Laundry detergent	0.01–1.0	0.01–1.0				
Dishwashing liquid	0.01–1.0	0.01–1.0				
Disinfectant	<1					

Leather wipes		<1	<1		
Surface cleaner	<1	<1	<1		
Glass cleaner	0.01–1.0	0.01–1.0			
Wood cleaner	<1	<1			
Floor cleaner	<0.1–1.0	<0.1–1.0			
Carpet cleaner	<0.1	<0.1			
Ink cartridge	<1				
Body lotion		<1			
Hand wash	<1	<1			
Exterior wall paint					0.1–1.0
Exterior floor paint		<0.09	<0.09		
Interior ceiling paint		<0.09	<0.09		
Interior wall paint primer		<0.09	<0.09		

		Range of concentration (ppm) (Aerts et al., 2015)			
Water-based wall paints	23–41	8–225			
		Range of concentration (ppm) (Lundov et al., 2014)			
Wall paints	1.5–360	10–300	2–14		
		Paint products in Australia (range of concentration (% w/w))*			
Paints used in industrial/factory/ automotive	0.0003–0.03	0.00002–0.00398		0.00032	0.00266
Paints used in DIY/ professional painter for residential/ commercial structures	0.00359–0.08806	0.005687–0.018242	0.0001–0.0015	0.00032	0.00007–0.11952

* Data provided by the Australian paint industry.

Information on uses has been obtained from online searches, reports and databases, including:

- Galleria Chemica;
- the European Commission Cosmetic Ingredients and Substances (CosIng) database;
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- the US Department of Health and Human Services Household Products Database (HPD);
- the US National Library of Medicine's Hazardous Substances Database (HSDB);
- US Environmental Protection Agency's (EPA) Aggregated Computational Toxicology Resource (ACToR);
- the Environmental Working Group Skin Deep cosmetics database;
- the Cosmetic Ingredient Review (CIR) Expert Panel Safety Assessments;
- the Substances and Preparations in Nordic countries (SPIN) database;
- the Skin Carisma database;

- the Scientific Committee on Consumer Safety (SCCS) assessments;
- the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) assessments;
- the Irish Department of Agriculture, Fisheries and Food's Biocidal Products Register; and
- the Danish Ministry of the Environment's Survey of Biocidal Products in Denmark.

Appendix 2

Table A2. Published retrospective and prospective studies of skin sensitisation to isothiazolinones.

Reference	Brief method description	Results
Weaver et al., 1985	Human volunteers (n=9) in the USA, who had developed delayed contact hypersensitivity to MCI/MI mixture (Kathon® CG, CG/ICP), participated in diagnostic use tests and diagnostic threshold patch tests. The continued hyperreactivity was confirmed through positive reactions to diagnostic patch testing with MCI/MI mixture (100 ppm aqueous (aq.)) before threshold patch testing began. Volunteers used personal care products (shampoo, soap, conditioner, fabric softener, bath foam) for 3–6 weeks. They kept daily diaries to record their continued use. The patches remained on the skin for 48 hours. Threshold patch testing used concentrations of 1, 2, 5, 10, 15, 25 and 50 ppm aqueous. These concentrations were in addition to the pre-use test screening patch testing of 100 ppm.	• 9 subjects were available for diagnostic threshold patch testing after the product use period. The remaining subjects were unavailable for this testing for personal reasons unrelated to the test materials. • None reacted to concentrations of 1, 2, 5, 10 or 15 ppm. • 1 subject reacted to 25 ppm. • 5 subjects reacted to 50 ppm. • 3 remaining subjects reacted only to the 100 ppm concentration that had been used initially to confirm their continued hypersensitivity to MCI/MI mixture.

Reference	Brief method description	Results
Fischer et al., 1995	202 painters (200 men, 2 women) from painting companies aged 16–65 years old participated. Painters were interviewed, examined and patch tested by dermatologist. Patch test included a standard series and a test series prepared from ingredients of modern water-based paints, glues and putties. Patch tests were evaluated according to international standards at 3 days after application and 1 day after removal of patches. Concentrations used in the patch test series (vehicle type): ● 0.1 % benzisothiazolinone (BIT) (petrolatum) ● 0.1 % 2n-octyl-3-isothiazolinone (OIT) (petrolatum). ● 48 painters had a history of eczema, 31 of these had current problems. ● 25 had a history of hand eczema, 16 with ongoing disease. ● 14 had a history of previous severe hand dermatitis. ● 11 of 25 work was main cause of disease. ● Skin conditions included erythema, itching, skin dryness, dry fissuring of the knuckles and fingers, and tylosis.	Patch test results: ● 7 positive to BIT (2 related to work). ● 1 positive to OIT related to work. ● 5 positive to MCI (concentration unspecified) (3 related to work).

Reference	Brief method description	Results
Chew and Maibach 1997	56 adult healthy volunteers were patch tested using the following BIT and Proxel® GXL formulation (contained 20 % BIT in aq. propylene glycol): • 0.002 % BIT in aq. dipropylene glycol (0.01 % aq. Proxel® GXL) • 0.01 % BIT in aq. dipropylene glycol (0.05 % aq. Proxel® GXL) • 0.1 % BIT (petrolatum). Patch test used Finn Chambers for solid or liquid (17 µL), or Finn Chamber pads for liquids. Patches remained for 2 days, and read at day 3 and 4.	• 10 of 56 had positive reactions to 0.1 % BIT at 4 days. 9 of the 10 were negative after retesting, which suggests sensitisation was not induced under the conditions. The 10th showed macular erythema, suggestive of irritation. • No evidence of irritation or allergic reaction to 0.01 % and 0.05 % Proxel®.
SCCNFP, 2004	15 healthy volunteer patients (2 males, 13 females, aged 25–66 years old) were recruited for a randomised double blind open epicutaneous application study. They were previously diagnosed with sensitisation to MCI. Test cream used was Doublebase containing 0.3 % (w/w) (150 ppm) of Microcare® SI (containing 0.15 % (w/w) BIT and 0.15 % MI). Subjects were instructed to apply twice daily for 4 weeks 1–1.5 mL of test cream to the inner aspects of both forearms, and complete a diary of usage. The test cream were weighed at the end of the study.	• 10 subjects completed the study, 2 subjects were lost to follow-up and 3 withdrew due to eczema on the forearms that were considered to be related to Microcare® SI. • 9 out of 10 subjects had no visible redness after 4 weeks of application. • 1 out of 10 had distinct redness. • Without unblinding the study, the authors concluded that Microcare® SI can be tolerated by some, but not all subjects previously sensitised to MCI.

Reference	Brief method description	Results
Geier et al., 2004	The Information Network of Departments of Dermatology (IVDK) data of 251 (of 16848) metalworkers with suspected metalworking fluid (MWF) dermatitis, were retrospectively reviewed. The test series used were current and historical MWF allergens, and the German Contact Dermatitis Research Group (DKG) standard series. Patch tests were performed and read according to the International Contact Dermatitis Research Group (ICDRG) and the DKG guidelines. Concentrations used in patch test and number of patients tested: ● OIT (0.025 % in petrolatum) (199 patients) ● 1,2-Benzisothiazolin-3-one, sodium salt (0.1 % in petrolatum) (152 patients) ● MCI/MI (0.01 % aq.) (214 patients). ● 231 men (92.0 %) (age range 17–62 years, median 38 years old).	Patch test reactions: ● OIT: 1 % of 199 tested positive (95 % CI 0.1–3.6). ● 1,2-Benzisothiazolin-3-one, sodium salt: 2 % of 152 tested positive (95 % CI 0.4–5.7). ● MCI/MI: 4.2 % of 214 tested positive (95 % CI 1.9–7.8).

Reference	Brief method description	Results
Aalto-Korte et al., 2007	From 1991–2005, patients in Finland with allergic reactions to OIT were retrospectively reviewed. Total of 2222 patients were patch tested with OIT. Patch testing used an in-house or a commercial preparation. 0.1 % OIT (petrolatum) was used.	• 8 (0.004 %) had allergic reactions to OIT (commercial preparation). • Occupations of the 8 patients positive to OIT were paint manufacturer worker, machinist, dairy farmer and sewing machine operator. • The sewing machine operator worked in a mattress manufacturer where she experienced dermatitis on her hand. She was also allergic to MCI/MI and other chemicals. • OIT was detected in the mattress textile samples.
Uter et al., 2013	Retrospectively reviewed IVDK data from 56 dermatology departments in Germany, Switzerland and Austria. From 2009–2012, 28922 patients were patch tested with MI 0.05 % (500 ppm, aq.) contained in the cosmetic preservatives series. MCI/MI were tested at 100 ppm in the baseline series in 28042 patients.	• The prevalence of positive patch test reactions to MI was 3.83 % (95 % CI 3.62–4.06 %). • Of all positive reactions, 56.4 % were weakly positive (+), 33.9 % were strongly positive (++), and 9.7 % were extremely positive (+++). • 1.4 % reacted to MI, but not to MCI/MI. • 1.6 % reacted to MCI/MI, but not to MI. • 2.3 % reacted to both MI and MCI/MI.

Reference	Brief method description	Results
Aerts et al., 2014	From 2010–2013, 6599 patients in Belgium were retrospectively reviewed for MCI/MI, MI, BIT and OIT sensitisation. In 2013, additional 2081 patients were also reviewed. Patch tests were performed according to the ICDRG guidelines. Concentrations used: • 100, 200 ppm MCI/MI (aq.) • 200, 500, 1000, 2000 ppm MI (aq.) • 0.05 % BIT (in petrolatum) • 0.1 % OIT (in petrolatum)	• Rate of contact sensitisation to MCI/MI increased from 3.6 % in 2010, to 3.7 % in 2011, and to 4.5 % in 2012. • In 2013, MCI/MI sensitisation significantly increased to 5.3 %. • Rate of sensitisation to MI alone increased from 3.1 % in 2010, to 6.0 % in 2012, and to 7.2 % in 2013. • Of those that reacted positively to MCI/MI and/or MI, 194 were tested with BIT, and 199 tested with OIT (8 tested with both BIT and OIT). • 4 reacted only to BIT • 23 reacted only to OIT. • Cosmetics were the most important allergen sources. • Non-cosmetic sources of exposure were mainly household detergents, the frequency of which doubled from 4.1 % in 2010 to 8.7 % in 2012, and paints. • 31 of 55 work-related allergen sources were industrial products, and the rest were cosmetics. • In 29 of 335 (8.7%) patients who reacted to MCI/MI and/or MI, an airborne exposure was present, in all cases but 1 (roofing material) caused by water-based paints. • 19 of 35 cases were relevant allergen sources for BIT and OIT (11 occupational, 8 non-occupational sources e.g. paints, detergents, oils and cooling fluids).

Reference	Brief method description	Results
Vauhkala et al., 2015	From 2002–2013, patients in Finland with occupational contact allergy to MCI/MI and MI were retrospectively reviewed. Patch testing used the modified Finnish baseline series with Finn Chambers according to the ICDRG. Concentrations used in the patch test: • 0.01 % or 0.02 % MCI/MI (aq.) • 0.03 % or 0.1 % MI (aq.) • 0.1 % OIT (petrolatum) • 0.05 % BIT (petrolatum) Patches were read 2–3 times on days 2–6.	• 1745 patients were patch tested, 72 (4.1 %) showed an allergic reaction to MCI/MI and/or MI. • 45 (2.6 %) patients were positive to MCI/MI • 24 (1.4 %) patients were positive to both MCI/MI and MI • 3 (0.2 %) patients were to MI only. • 36 (50 %) cases of MCI/MI and/or MI contact allergy were considered to be occupationally related. • Of the 36 patients, 2 (5.5 %) also had contact allergy to BIT, and 4 (11 %) to OIT. • Occupations included beauticians, mechanics, machinists, painters, paint factory workers and cafe/restaurant workers.
Madsen and Andersen, 2016	From 2002–2015, patch test results from eczema patients tested with BIT (0.1 % and 0.05 % in petrolatum) in Denmark were retrospectively reviewed. Patch tests used Finn Chambers. Patch tests were read on day 3, 4 and 7.	• 392 patients were tested with 0.05 % BIT and 183 with 0.1 % BIT. • 27 patients had positive patch test reactions to 0.05 % and/or 0.1 % BIT. Most patch test reactions were weakly (+) or moderately (++) positive on day 3/4, and only 1 negative patch test reaction turned positive on day 5/7. • 8 patients were patch tested simultaneously with both 0.05 % and 0.1 % BIT, 4 had positive reactions to both. • 4 had negative reactions to 0.05 % BIT, but positive (+) to 0.1 % BIT. • Of the positive reactions to BIT, 85 % were men, 67 % had hand eczema, and 63 % were occupationally related.

Reference	Brief method description	Results
Zirwas et al., 2017	From 2013–2014, 4860 patients from 13 centres of the North American Contact Dermatitis Group (NACDG) were retrospectively reviewed. Patch test used a series of 70 allergens including 0.2 % MI (aq.) and 0.01 % MCI/MI (aq.). Patch tests were read according to the NACDG guidelines.	• 305 positive reactions to MCI/MI (6.3 %). • 521 positive reactions to MI (10.7 %). • Positive reactions to MCI/MI significantly increased compared with 5 % in 2011–2012. • 246 patients reacted to both MCI/MI and MI (5.1 %). • 59 patients (1.2 %) had a reaction to MCI/MI alone. • 275 patients (5.7%) had a positive reaction to MI alone.
Ljubojević Hadžavdić et al., 2018	From 2015–2016, dermatitis patients diagnosed with MI contact allergy who were patch tested in a Croatian dermatology department were retrospectively reviewed. Patch testing used the Croatian baseline series with 8 mm Finn Chambers. Applied 15 µL each of MI (0.2 % aq.) and MCI/MI (0.01 % aq.) onto filter paper in a Finn Chamber. Patches were read on day 2, 3 and 7 according to the European Society of Contact Dermatitis guideline.	• 798 patients (198 males, 600 females) were tested with the baseline series. • Of these, 51 (6.4 %) reacted positively to MCI/MI. • 105 (13.2 %) reacted positively to MI. • 40 (5 %) patients reacted positively to both MI and MCI/MI. • 116 (14.5 %) patients reacted positively either to MCI/MI or MI. • The main occupations were office workers, students, pensioners and housewives. Only 1 was a painter. • The most frequent products found to be relevant for current dermatitis were dish washing liquid and laundry detergent. Wall paint is the 10th frequent product. • The main product groups in the context of private exposure were wet wipes, liquid soaps, shampoos, bath/shower gels and hand creams.

Table A3. Case reports of allergies to isothiazolinones in various products are summarised in the table below.

Reference	Description
Mathias et al., 1983	• 31-year-old male developed recurrent dermatitis 6 weeks after commencing employment as a batch maker for a paint manufacturing company. Batches of paint involved addition of mildewcide (Skane M-8® containing OIT), which he poured into a mixer from a small bucket. Multiple eczematous blotches and streaks were observed on the forearms and wrists. • Patch testing was performed according to the ICDRG. • Patch test used 0.05 % Skane M-8® (0.045 % OIT and 0.005 % impurities in propylene glycol) and in petrolatum. • A strong positive (+++) reaction to SkaneM-8® was observed at 48 and 96 hours. • Allergic contact dermatitis to Skane M-8® was diagnosed.
Bohn et al., 2000	• 5 case reports of women experiencing allergic symptoms including dermatitis, erythema and eczematous macules when exposed to freshly painted or renovated homes. • Patch testing used the European standard series. • Emissions from paint and varnish samples were measured by HPLC. • In the wall and ceiling paint and in the varnish from patient 1, MCI/MI was measured at concentrations of 5–28.4 mg/kg. Emission of MCI/MI from paint was detected from wet as well as from dried glass surfaces. • Air concentrations of MCI released from paint at the beginning were 80 µg/m^3 and still 5 µg/m^3 after 4 weeks. • Patient 1 and 2 had positive reactions (+++) to MCI/MI. • Patient 4 and 5 had positive (++) reaction to MCI/MI. • Patient 3 had positive reaction MCI/MI without grading.

Reference	Description
Walker et al., 2004	• 47-year-old had a bilateral hyperkeratotic palmar dermatitis for 8 months. He made water-based varnishes, the components of which frequently came into contact with his hands. There had been a rapid improvement in the hand dermatitis when he took 2 weeks off work, but on returning to the same job the dermatitis had flared rapidly. He also had a history of an exacerbation of his hand dermatitis following direct application of Oilatum® Plus bath additive (triclosan 2% and benzalkonium chloride 6%, both of which can cause allergic contact dermatitis) to his skin. • Patch testing used a standard series, his own medicaments, gloves and components of face, eye and coolant series. He had positive (++) reactions to 0.05 % BIT (petrolatum) and 0.1 % benzalkonium chloride (petrolatum).
Thyssen et al., 2006	• Between 2004–2005, a factory outbreak of occupational contact dermatitis at a Danish paint factory was reported. At the paint factory, one additive introduced contained 7–10 % MI and 1–2.5 % OIT. Another product which contained 0.2–0.4 % MI and 0.5–1 % MCI. A third product contained 2.5 % MI and 2.5 % BIT. • 4 patients had dermatitis following introduction of these additives. • Patch tested with a paint test series at the following concentrations: • MCI/MI (0.01 %, aq.) • MI (0.105 %, aq.) • BIT (0.05 %, petrolatum) • OIT (0.1 %, petrolatum). • Patch test results from all patients in this factory outbreak showed positive reactions to MI and MCI/MI. The reactions were stronger for MI than for MCI/MI indicating primary sensitisation to MI. • 3 patients had positive patch tests to OIT. • 1 patient had a positive patch test to BIT.

Reference	Description
Kaae et al., 2012	• 23-year-old non-atopic previously healthy woman with facial dermatitis. Symptoms began 2 months after she started working in a restaurant where the walls had just been painted. She began to suffer from periorbital oedema, which progressed to vesicular dermatitis. The greater the number of consecutive days that she worked in the restaurant, the more the symptoms were aggravated, but they improved when she was off work. • Patch testing was performed with the European baseline series, an extended patch test series including the patient's own cosmetic products, and an extended series of fragrance ingredients. • Patch testing was performed according to the ICDRG. • Positive patch test reactions to MCI/MI (++) (0.01 % aq.) and MI (++) (0.2 % aq.) were observed, as well as to other metals.
Gilmore et al., 2017	• Male patient, in his 60s, had a rash involving multiple areas of the body, for over 3 years. He was retired and his hobbies included gardening and landscaping work. His personal care products contained MI. • Diagnosed with allergic contact dermatitis, irritant contact dermatitis and endogenous eczema. • Patch testing used the North American Contact Dermatitis Group standard series and preservative series. • Patch test was scored according to the ICDRG. • He had a 3+ positive reaction to MI and a 2+ reaction to Kathon® CG (MCI/MI).

Reference	Description
Van Steenkiste et al., 2015	• 58-year-old non-atopic woman experienced an eruption on the face and neck that had started a few years earlier with erythematous patches around the face. She had applied cosmetic products and noticed exacerbation when exposed to sunlight or applied sunscreens. • She was diagnosed with peri-ocular dermatitis. • A skin biopsy showed discrete spongiosis and parakeratosis, and a limited lymphocytic and plasmocytic perivascular infiltrate in the upper dermis; this was interpreted as chronic eczema. • Patch test used the European baseline series with IQ Ultra® Chambers, a cosmetic series and her own products. • Concentrations used in the patch test were: • 500, 2000 ppm MI (aq.) • 100 ppm MCI/MI (aq.) • 0.05 % BIT (petrolatum) • 0.1 % OIT (petrolatum). • Positive reaction to 2000 ppm MI. • Positive reactions to her own sunscreen and cosmetic products. • HPLC analysis showed the presence of MI (at 181.3 ppm) and BIT (at 4.6 ppm) in a detergent product used at home, which may have also caused her eczematous lesions.
RAC, 2018a	• 8 out of 19 workers at a textile finishing factory developed itchy reddish eruptions on exposed areas of skin. About 3 weeks prior to the occurrence of dermatitis, a new biocide (containing 30 % DCOIT as the active ingredient in xylene) was introduced to the finishing agent. • Open patch test was performed on 6 patients with the finishing agent with 0.2 % biocide (0.06 % (600 ppm) DCOIT) and the finishing agent without the biocide. Applied onto a 2 cm^2 area of skin on the upper arms (volume of elicitation test and induction dose unspecified). • 5 out of 6 patients showed a strong positive reaction to the finishing agent with biocide, none showed any reaction to the finishing agent without the biocide. • 1 patient showed no reaction to either finishing agent with or without the biocide, but this person had taken corticosteroids 2 days prior to the patch test.

Table A4. Human patch tests for isothiazolinones are summarised in the table below.

Reference	Description of study	Results
	MI	
RAC, 2016a	HRIPT Test substance: 50 % MI (in propylene glycol) Total number of subjects tested: 836 Induction and challenge concentrations: 0.01, 0.02, 0.03, 0.04, 0.05 and 0.06 % MI (100, 200, 300, 400, 500, 600 ppm MI, respectively)	• Number of subjects sensitised: • 0.01 % (3.75 µg/cm^2) (1/98) (presensitised individual) • 0.02 % (10 µg/cm^2) (0/100) • 0.03 % (15 µg/cm^2) (0/98) • 0.04 % (20 µg/cm^2) (1/116) • 0.05 % (25 µg/cm^2) (1/210) • 0.06 % (30 µg/cm^2) (0/214)
	21-day cumulative insult patch test Total number of subjects tested: 16 Concentrations: 0.005, 0.01, 0.025, 0.05 and 0.1 % MI (50, 100, 250, 500 and 1000 ppm MI, respectively) 19 mm Hill Top chambers	• Number of subjects sensitised: • Induced and challenged: 0.1 % (2/16)
	BIT, MCI	

Reference	Description of study	Results
Basketter et al., 1999	HRIPT data for BIT were obtained from a historic Zeneca database with limited information on the patch test method used. HRIPT data on MCI were from published literature. Concentrations used and number of subjects: • 20 ppm MCI (aq.) (45 subjects) • 12.5–15 ppm MCI (various vehicles) (284 subjects) • 10 ppm MCI (aq.) (175 subjects) • 725 ppm BIT (aq.) (58 subjects) • 360 ppm BIT (aq.) (54 subjects) For BIT, analysis was complicated by the presence of 1,2-ethanediamine which is also a skin sensitiser.	• Number (percentage) of subjects sensitised: • 20 ppm MCI (2/45 (4.4 %)) • 12.5-15 ppm MCI (1/284 (0.4 %)) • 10 ppm MCI (0/175 (0 %)) • 725 ppm BIT (5/58 (9 %)) • 360 ppm BIT (0/54 (0 %). • MCI threshold concentration for skin sensitisation was 12.5–20 ppm. • For BIT, the authors considered that the realistic no effect level was about 500 ppm, based on the conservative assumption that the reactions were all due to BIT (rather than 1,2-ethanediamine).
OIT		
RAC, 2018b	21-day cumulative insult patch test OIT at concentrations of 100, 250, 500, or 1000 ppm (in petrolatum and Tween-85) were applied in Finn Chambers daily for 21 days to male and female volunteers. After 21-day test, any volunteer with suspected sensitisation reaction was challenged at a distant skin site. Challenge patches were left in place for 48 hours.	Confirmed sensitisation reactions occurred in 1/20 subjects induced/challenged with 500 ppm (0.05 %) OIT and in 5/20 volunteers with up to 1000 ppm (0.1 %) OIT.

Reference	Description of study	Results
	HRIPT An aqueous solution of OIT (50 ppm, 0.2 mL) was applied to an occluded patch measuring 2 x 2 cm. Dose was 0.0025 mg/cm^2.	No sensitisation reactions in 103 subjects induced and challenged with 50 ppm (0.005 %) OIT.
	HRIPT An aqueous solution of OIT (100 ppm, 0.2 mL) was applied to an occluded patch measuring 2 x 2 cm. Dose was 0.005 mg/cm^2.	Confirmed sensitisation reaction in 1/222 subjects induced and challenged with 100 ppm (0.01 %) OIT.
	HRIPT Solution of OIT in body lotion (100 ppm, 0.2 mL) was applied to an occluded patch measuring 2 x 2 cm. Dose was 0.005 mg/cm^2.	Sensitisation reactions in 3/222 subjects induced and challenged with 100 ppm (0.01 %) OIT in body lotion. Re-challenge was conducted in 1 of these subjects and sensitisation was confirmed.
	DCOIT	
RAC, 2018a	HRIPT Individuals not previously sensitised were exposed to 0.2 mL of 0.025 % or 0.035 % DCOIT (in ethanol) during induction phase (3 times per week for 3 weeks, 34 subjects/dose level). After 2 weeks rest period, naïve sites were challenged for 24 hours with 0, 0.01, 0.025 or 0.035 % DCOIT (in ethanol).	• Sensitisation was observed in: • 4/34 (12 %) of subjects induced with 0.025 % DCOIT • 14/34 (41 % subjects) induced with 0.035 % DCOIT. • The lowest level tested inducing sensitisation (0.025 %) corresponds to 12.5 µg/cm^2.

Reference	Description of study	Results
	As a follow-up of the HRIPT study, 8 subjects that responded positively to induction and challenge with 0.035 % DCOIT were re-challenged 6 months later in a 24 hours occlusive patch test, with 0 % DCOIT (ethanol) or 0.025 % DCOIT (in ethanol).	• 3 of the 8 subjects responded positively to re-challenge with 0.025 % DCOIT, with a lower, higher, or similar intensity than they did in the initial challenge approximately 6 months earlier. Possible explanations for these results may be that the number of sensitisation responses in the previous study may have been irritant responses, or that the intensity of the elicitation response in DCOIT-sensitised subjects decreased over time.
	24 and 48-hour occlusive patch tests were performed in 10 subjects with 0.035, 0.05, 0.075 or 0.1 % DCOIT (in ethanol). Applied 0.01 mL on 8 mm circular chamber discs. The time point for dermal examination was not stated, but it may have been performed immediately after patch removal.	• No distinct differences in irritation between the 4 concentrations were observed. However, 2 subjects (20 %) reacted adversely to all test concentrations of DCOIT and still exhibited reactions 10–15 days after patch removal, suggesting a sensitising activity to the agent. The study included few individuals and the lowest exposure level induced effects. The lowest dose tested giving positive effects (0.035 %) corresponds to 7 µg/cm^2.

Table A5. Skin sensitisation studies in animals.

Reference	Description of study	Results
	MCI/MI and MI	

Reference	Description of study	Results
RAC, 2016b	Open epicutaneous test (non-guideline) Dunkin Hartley guinea pigs (8 females/group) Test substance active ingredient (a.i.): 14 % MCI/MI (in ethanol/aqua bidest) Induction: 0.1 mL at 0, 0.021, 0.04, 0.08, 0.25, 2.5 and 5 % a.i. (corresponding to 0, 30, 58, 115, 360, 3600 and 7200 ppm, respectively) First and second challenge: 0.025 mL at 0, 0.021, 0.04, 0.08, 0.25, 2.5 and 5 % a.i. (corresponding to 0, 30, 58, 115, 360, 3600 and 7200 ppm, respectively) First challenge occurred 3 days after 20th induction, and the second challenge occurred 14 days after the first challenge.	• Sensitiser First challenge: • 8 no reactions at 0.021, 0.04 and 0.08 % a.i. • 1/8 positive reaction at 0.25 % a.i. • 6/8 positive reactions at 2.5 % a.i. • 6/8 positive reactions at 5 % a.i. Second challenge: • 32 no reactions induced and/or challenged at 0.021 % a.i. • 8 no reactions induced and challenged at 0.04 % a.i. • 1/8 positive reaction induced and challenged at 0.08 % a.i. • 3/8 positive reactions induced and challenged at 0.25 % a.i. • 8/8 positive reactions induced and challenged at 2.5 % a.i. • 7/8 positive reactions induced and challenged at 5 % a.i.
	GPMT Buehler test (non-guideline) Dunkin Hartley guinea pigs (5-10/sex/group) Test substance (a.i.): 14 % MCI/MI (aq., prepared from Kathon™ 886) Induction: 0.0025, 0.005, 0.01, 0.05 and 0.1 % a.i (corresponding to 25, 50, 100, 500 and 1000 ppm, respectively) Challenge: 0.002, 0.0025, 0.005, 0.01, 0.02, 0.025, 0.05, 0.1 and 0.2 % a.i (corresponding to 20, 25, 50, 100, 200, 250, 500, 1000, and 2000 ppm, respectively)	• Sensitiser • Induction at 0.01 % a.i.: 1/15 and 9/15 positive reactions at 0.01 and 0.2 % a.i. challenge concentrations, respectively. • Induction at 0.05 % a.i.: 0/10, 3/10 and 10/10 positive reactions at 0.01, 0.05 and 0.2 % a.i. challenge concentrations, respectively. • Induction at 0.1 % a.i.: 0/20, 3/15, 3/5, and 4/5 positive reactions at 0.005, 0.02, 0.05 and 0.1 % a.i. challenge concentrations, respectively.

Reference	Description of study	Results
		• Not sensitiser Challenge: • Induction at 0.003 % a.i.: 1/19 grade 1 reaction at 0.003 % a.i. challenge concentration • Induction at 0.005 % a.i.: 19 no reactions Re-challenge: • Induction at 0.003 % a.i.: 1/19, 1/19, 1/19 grade 1 reactions at 0.005, 0.01, 0.02 % a.i. challenge concentrations • Induction at 0.005 % a.i.: No reactions at 0.005 and 0.01 % a.i. challenge concentrations • Induction at 0.005 % a.i.: 3/19 grade 1 reactions at 0.02 % a.i. challenge concentration • 1 animal died considered to be unrelated to treatment
	GPMT (Magnusson and Kligman) (OECD 406) Dunkin Hartley guinea pigs (20 females/group) Test substance (a.i.): 14 % MCI/MI (aq.) Induction: 0.003 and 0.005 % a.i. (30 and 50 ppm) Challenge: 0.003 and 0.005 % a.i. (30 and 50 ppm) Re-challenge: 0.005, 0.01 and 0.02 % a.i. (50, 100 and 200 ppm)	
		• Sensitiser Challenge: • 3/10 positive reactions at 0.355 % a.i. challenge concentration • 5/10 at 0.71 % a.i. • 10/10 at 1.07 % a.i. • 10/10 at 1.42 % a.i. Re-challenge: • 0/10 at 0.000355 % a.i. • 4/10 at 0.00355 % a.i.
	GPMT (Magnusson and Kligman) (OECD 406) Dunkin Hartley guinea pigs (10 females/group) Test substance (a.i.): 14 % MCI/MI (aq.) Induction: 0.71 % (intradermal) and 3.55 % a.i. (topical) Challenge: 0.355, 0.71, 1.07, 1.42 % a.i. (3550, 7100, 10700 and 14200 ppm) Re-challenge: 0.000355 and 0.00355 % a.i. (3.6 and 36 ppm)	

Reference	Description of study	Results
	LLNA (OECD 429) CBA/J mice (5 females/group) Test substance (a.i.): 14 % MCI/MI (acetone/olive oil, 4:1) Induction: 0, 0.003, 0.005, 0.007, 0.009, 0.036 and 0.1 % a.i. (corresponding to 0, 30, 50, 70, 90, 360, 1000 ppm, respectively)	• Sensitiser • SI ≥3 at concentrations ≥0.003 % a.i.
	LLNA (OECD 429) CBA/J mice (5 females/group) Test substance (a.i.): 14 % MCI/MI (aq.) Induction: 0.003, 0.005, 0.007, 0.009, 0.036 and 0.1 % a.i. (corresponding to 0, 30, 50, 70, 90, 360, 1000 ppm, respectively)	• Sensitiser • SI ≥3 at concentration ≥0.007 % a.i.
RAC, 2016a	GPMT Buehler test (OECD 406) Hartley guinea pigs Test substance: 99.8 % MI Induction: 0.1, 0.5, 1.5 and 3 % MI (corresponding to 1000, 5000, 15000 and 30000 ppm, respectively)	• Sensitiser • Challenge at 0.1 % MI: 0/10, 0/10, 1/10 and 0/10 positive reaction, respectively. • Challenge at 0.5 % MI: 0/10, 2/10, 1/10 and 2/10 positive reactions, respectively. • Challenge at 1.5 % MI: 1/10, 6/10, 3/10 and 5/10 positive reactions, respectively.

Reference	Description of study	Results
	GPMT (Magnusson and Kligman) (OECD 406) Hartley guinea pigs Test substance: 99.7 % MI Induction: 0.055, 0.08 % MI (550 or 800 ppm) Challenge: 0.05, 0.08 % MI (500, 800 ppm). Re-challenge: 0.1 % MI (1000 ppm)	• Not sensitiser Challenge: • No reactions at 0.055 and 0.08 % MI induction and challenge concentrations Re-challenge: • Induction at 0.055 % MI: 4/20 dermal reaction at 0.1 % MI re-challenge • Induction at 0.08 % MI: 5/19 responded to 0.1 % MI re-challenge
	GPMT (Magnusson and Kligman) (OECD 406) Dunkin-Hartley guinea pigs Test substance: Acticide SR (purity: 49 % a.i. in water) First induction: 0.1 % (intradermal) Second induction: 10 % (topical) Challenge: 1 % (topical)	• Sensitiser • 10/10 positive reactions
	LLNA (OECD 429) CBA/J mice Test substance: 10.37 % MI (in water)	• Sensitiser • SI ≥3 at concentrations at 1.35 %
	LLNA (OECD 429) CBA/J mice Test substance: 99.9 % MI	• Not sensitiser • SI <3
	BIT, MCI and MI	

Reference	Description of study	Results
Botham et al., 1991	LLNA (non-guideline) CBA/Ca mice (4/group) 25 µL of test substance applied to the ears. Vehicle used for BIT, 5-chloro-2-methyl-4-isothiazolin-3-one (MCI) and 2-methyl-4,5-trimethylene-4-isothiazolin-3-one (MI): dimethyl formamide Concentrations used: **BIT** • First and second experiments: 0, 3, 10, 30 and 50 % (w/v) **MCI** • First experiment: 0, 3, 10, 30 and 50 % (w/v) • Second experiment: 0, 0.3, 1 and 3 % (w/v) • Third experiment: 0, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3 and 1 % (w/v) **MI** • First experiment: 0, 3, 10, 30 and 50 % (w/v) • Second experiment: 0, 0.3, 1, 3 and 10 % (w/v)	BIT, CMI, and MI are Sensitisers • Lowest concentration (LC%) to give ≥3-fold increase in test animals compared to vehicle-control group for BIT, MCI and MI: 10 %, 0.01 % and 3 %, respectively. • Calculated EC3 = 250 x (LC%/100) • BIT EC3: 25 µg/cm^2 • MCI EC3: 0.025 µg/cm^2 • MI EC3: 7.5 µg/cm^2

Reference	Description of study	Results
SCCNFP, 2004	GPMT (OECD 406) Albino Dunkin Hartley guinea pigs (n=20 (test), 10 controls, 8 range-finding) Test substance: 79.8 % BIT (in water), 19.2 % diamide Vehicle: corn seed oil (induction), Freunds Complete Adjuvant/water (0.1 % induction), ethanol (challenge) Induction concentrations used: 0.1 % (w/v) (intracutaneous) and 20 % (epicutaneous, occlusive). Challenge concentration: 10 % (w/v) (epicutaneous, occlusive)	• Sensitiser • 9/20 animals reacted positively to 10 % BIT (challenge), response incidence of 45 %.
	GPMT Buehler test (EPA OPP 81-6) Albino Hartley guinea pigs (n=30 (test), 8 range finding) Vehicle: corn seed oil Test substance: Nuosept BIT technical (purity: 82.3 % BIT, 17.7 % water) Induction: 0.3 g of test substance (concentration 5 %) every week for 3 weeks Challenge: 14 days after last induction with same dose as induction	• Not a sensitiser • No reaction observed at any test or naïve control site following challenge.
SCCS, 2012	No experimental details available.	• EC3: 2.3 % BIT
	OIT	

Reference	Description of study	Results
RAC, 2018b	LLNA (OECD 429) CBA/CaOlaHsd mice (4 females/dose) Concentrations used: 0.25, 0.5, 2.5, 4 and 5 % OIT (purity: 97.6 %, in acetone:olive oil, 4:1 (v/v))	• Sensitiser • SI ≥3 at concentrations ≥0.5 % • EC3: 0.46 % (w/v)
	LLNA (OECD 429) CBA/J mice (5 females/dose) Concentrations used: 0, 100.6, 320.4, 1036.6, 3062.1 and 11250 ppm OIT (purity: 99.8 %, in acetone)	• Sensitiser • SI ≥3 at concentrations ≥11250 ppm • EC3: 0.66 % (w/v)
	LLNA (non-guideline) CBA/J mice (6 females/dose) Concentrations used: 100, 300, 1000, 3000 and 10000 ppm OIT (purity 99.32 %, in acetone). No positive control.	• Sensitiser • SI ≥3 at concentrations ≥3000 ppm • EC3: 0.24 % (w/v)

Reference	Description of study	Results
	GPMT Buehler test (OECD 406) Hartley albino (10/sex/concentration, 5/sex/controls) Vehicles used: ethanol (induction), acetone (challenge) Induction concentrations used: 25, 50, 100, 500, 750, 1200 and 2400 ppm OIT (48 % in propylene glycol) Challenge concentrations used: 100, 750 and 1200 ppm OIT (48 % in propylene glycol) No positive controls.	• Sensitiser • 20 % of animals positively responded to an induction at 50 ppm and challenge at 1200 ppm.
	GPMT (non-guideline) Dunkin/Hartley (20 females/concentration) Vehicle: Alembicol D Induction concentrations used: 1 % (intradermal) and 2.5 % OIT (topical) (48 % in propylene glycol) Challenge concentrations: 0.5 and 1 % OIT (48 % in propylene glycol)	• Sensitiser • 20/20 animals sensitised following 1 % challenge
	DCOIT	
RAC, 2018a	LLNA (OECD 429) Concentrations used: 0.005, 0.01, 0.1, 0.25 and 0.5 % (w/v) DCOIT technical (in acetone:olive oil, 4:1 (v/v))	• Sensitiser • EC3: 0.03 % (15 µg/cm^2)

Reference	Description of study	Results
	GPMT (OECD 406) Induction: Single dose 5 % DCOIT technical (in propylene glycol) (intradermal) Challenge 1: 25 % DCOIT (ethanol) Challenge 2: 5 % DCOIT (acetone)	• Sensitiser at ≥5 %
	GPMT (OECD 406) Induction concentrations used: 0.01, 0.02 and 0.03 % DCOIT technical (in mineral oil) (intradermal) Challenge: 0.01, 0.02 and 0.03 % DCOIT (topical)	• Sensitiser at ≥0.01 % (4.4 µg/cm^2)

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