Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

2-methylisothiazol-3(2H)-one (ISO)

EC number: 220-239-6
CAS number: 2682-20-4

CLH-O-0000001412-86-105/F

Adopted

10 March 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-METHYLISOTHIAZOL-3(2H)-ONE (ISO)

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 2-methylisothiazol-3(2H)-one (ISO)
EC number: 220-239-6
CAS number: 2682-20-4
Dossier submitter: Slovenia

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	United Kingdom	Confidential	Company-Manufacturer	1
Comment received				
The use of MIT in our product types has resulted in extremely rare amount of skin reactions. We therefore feel that the generic concentration limit of 0.1% is adequate in our experience for out products.				
Dossier Submitter's Response				
Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined. However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.				
RAC's response				
Noted; but the wider literature (and other public comments) indicates strongly that this limit is not adequate.				

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	United Kingdom	European Society of Contact Dermatitis	Scientific body	2
Comment received				
(i)The ESCD agrees to the classification of MIT as Skin sens. 1A, H317. (ii)The ESCD also agrees that the specific concentration limit should be lower than 0.1%,				

but **that the proposed specific concentration of 0.06% is not low enough to protect workers and consumers from skin sensitisation.**

(iii)The ESCD also agrees that a special labeling requirement is used for mixtures not classified as skin sensitisers, but containing MIT: 'Contains 2-methylisothiazol3(2H)-one. May produce an allergic reaction.' **However, the proposed concentration limit for the labelling (at 0.006%) is not low enough to protect sensitised workers and consumers from elicitation of allergic contact dermatitis.**

The proposed concentration limits for classification and labelling are based on old and sometimes insufficient data, and new investigations must be taken into account.

With regard to induction of sensitisation, the proposed classification seems to attach a great deal of importance to a human repeat insult patch test (HRIPT) study performed by Georgeian and Vendetti in 2002. No sensitisation was detected for the MIT concentration 0.06% when the final patch test with MIT was executed with the same concentration. Positive HRIPTs to 0.05% and 0.04% by the same author (Georgeian) in 2000 and 2001 are neglected. Furthermore, if the final patch testing had been performed with the recommended MIT concentration 0.2% (Bruze et al. Contact Dermatitis 2013:69:263-70), sensitisation might have been demonstrated for all HRIPTs presented in the proposal.

Studies have repeatedly demonstrated that MIT contact allergy is over-represented in painters. A recent study on preservatives including MIT in European paints reported the presence of MIT in 93% of the paints in the range 0.7 – 180.9 ppm (0.01809%) (Schwensen et al. Contact Dermatitis 2015:72:127-38). Thus, there are strong indications that MIT concentrations below 0.06% will sensitise.

The significance of aggregate exposure to MIT is also not considered with regard to sensitisation in the proposed Classification and Labeling document.

In a recent repeat open application test (ROAT) with 2 liquid hand soaps preserved with MIT at 100 ppm and 50 ppm, all volunteers sensitised to MIT tested positively to 100 ppm and 78% reacted to 50 ppm (Yazar et al. British J of Dermatology 2015:173:115-22). Thus, labeling at 0.006% (60 ppm) will not protect individuals allergic to MIT.

In conclusion, the ESCD suggests that MIT is classified as a sensitiser when present at a level of 15ppm or greater, and also labeled whenever used in a product individually or as a part of a mixture, or used to preserve a raw material and which results in a concentration of 1ppm or higher. This recommendation is aimed at protecting workers and consumers from contact allergy to MIT and allergic contact dermatitis from MIT

ECHA note: An attachment was submitted with the comment above. As it contains the same content as the comment, it is not provided as a separate attachment.

Dossier Submitter's Response

Considering the rising number of studies reporting increasing incidence of confirmed MIT sensitised individuals, skin sensitising reactions to MIT at doses below 600 ppm and wide use of MIT in industrial and consumer products, the weight evidence shows that 0.06 % concentration of MIT is not the satisfactory specific concentration limit for classification of MIT as Skin Sens. 1A,H317, to protect sensitised individuals from adverse health effects.

The human repeat insult patch test (HRIPT) on healthy human volunteers that is supporting our proposal for classification was performed with MIT concentrations up to 0.06

%. According to the Bruze *et al*. publication (2013), the proposed concentration of MIT that should be included in the European baseline series for skin sensitisation testing is 2000 ppm (0.2% w/w) in order to detect most of sensitised individuals.

On one hand we agree that at 2000 ppm a positive respose could have been observed at a higher rate compared to the tested doses by Georgeian (2002). On the other hand cases of skin sensitisation were reported in other studies at doses much lower than 2000 ppm. Therefore, the positive response would also have been expected at 600 ppm.

The aggregated exposure to MIT was not considered in the submitted dossier with regard to skin sensitisation since no consensus on the methodology for aggregated risk assessment for skin sensitisation has been established so far. In the SSCS opinion (June 2015) the model for quantitative risk assessment for MIT in cosmetic rinse-off products was included, even though the SCCS stated to have no faith in the model in its current form. Besides that, MIT is currently used in variety of professional and consumer products. According to our knowledge the exposure and risk for human health was estimated for the proposed use of MIT as PT 13 (metal working fluids) and for some cosmetic products. Conducting aggregated risk assessment for MIT is thus not possible due to insufficient information on the potential exposure to MIT from different uses.

We agree with the proposal that all products containing MIT should be labelled with EUH208 without in lower concentration lmit: "Contains 2-methylisothiazol-3(2H)-one. May produce an allergic reaction."

RAC's response

Thank you for the additional information in support of a lower concentration limit than that proposed by the Dossier Submitter. This is taken into account in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Sweden	Swedish Contact Dermatitis Research Group	Scientific body	3

Comment received

This answer is on behalf of the Swedish Contact Dermatitis Research Group, a scientific organisation with members who are experts in the field of contact dermatitis. It concerns the proposal for classification of MIT as skin sensitiser (H317), no other health hazards.

Manufacture and uses Section 2.2.2: In this section the report must state which products that MIT is used in and also in which concentrations. International scientific studies exist where products have been tested for MIT content (Schwensen et al 2015, Vauhkala et al 2015) and data from the Danish Product Register have been reported (Friis et al 2014), all showing MIT content in paint, hand cleansers, water-proofing material, detergents and skin care products generally in the range of a few ppm up to 400 ppm.

Dossier Submitter's Response

The current proposal for harmonised classification for MIT includes other health hazards:

Acute Tox. 3 (oral)	H301
Acute Tox. 3 (dermal)	H311
Skin corr. 1B	H314
STOT SE 3	H335
Eye Dam. 1,	H318

Regarding "Manufacture and uses" Section 2.2.2: for the purpose of this CLH dossier which presents an assessment of the hazardous properties of MIT and comparisons with classification criteria, providing additional data on uses and concentrations in this section is not required.

RAC's response
RAC concurs with the Dossier Submitter's response.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Luxembourg	Scientific Committee on Consumer Safety	EU regulatory committees	4

Comment received

ECHA Public consultation concerning CLH report:
Proposal for harmonised classification and labelling for 2- methylisothiazol-3(2H)-one.

Reply by Scientific Committee on Consumer Safety (SCCS)

Table of content

Summary and conclusion

The suggested CLP classification of 2-methylisothiazol-3(2H)-one (MIT) for skin sensitisation is category 1A (H317), with a specific concentration limit of ≥ 0.06%.

The SCCS finds that category 1A for MIT is justified based on the many cases of MIT sensitisation reported in the scientific peer-reviewed literature from consumer as well as occupational exposures and the continued and unprecedented steep increase in the occurrence of contact allergy to MIT in Europe. This human data is in accordance with animal studies showing that MIT is a potent sensitiser. The SCCS has adopted Opinions on sensitisation risks of methylisothiazolinone (SCCS/1521/13[1] and SCCS/1557/15[2]).

The SCCS agrees that a specific concentration limit (SCL) is needed. This is justified by the unusually high number of cases of sensitisation to MIT and reported continued increase in numbers of up to 6 fold among consumers and workers patch tested for MIT sensitisation in different areas of Europe. However, the suggested SCL of ≥ 0.06% (600 ppm) is considered too high to be sufficiently protective of consumers and workers and is not substantiated by animal or human data in the document.

It is well known that cosmetic products with up to 100 ppm MIT carry a significant risk of sensitisation. Paints are frequent causes of MIT sensitisation in workers and also in consumers. Currently the majority of water-based paints contain MIT in concentrations

below 100 ppm. In other chemical products for consumer and occupational use typical concentration below 100 ppm MIT is used too.

Exposures at the workplace will in many cases be similar to or worse than use of cosmetic products due to multiple applications, continuous exposures or product matrices, which may act as adjuvants for skin sensitisation. Skin sensitisation to MIT carries more severe consequences than usual for contact allergy, as MIT may evaporate from products and treated surfaces and by inhalation produce generalised contact dermatitis. In some cases respiratory symptoms has been reported. The limit for labelling following a SCL of 600 ppm will be 1/10 i.e. 60 ppm. Experimental data as well as clinical experience show that MIT sensitised individuals will react to very low levels of MIT such as a few ppm. The suggested SCL is too high to relevantly inform and protect the sensitised consumers or workers from severe allergic eczema and/or airborne contact dermatitis reactions.

The SCCS has assessed the risk of MIT in rinse-off cosmetic products and found that 15 ppm would be safe for the consumer from the view of induction of skin sensitisation (SCCS/1521/13 and SCCS/1557/15). Occupational use conditions and chemical exposures may be much more intense than consumer exposures to cosmetics.

Sensitisation to the mixture MCI/MIT has with increasing numbers of sensitised citizens to MIT, increased in parallel. An SCL already exists for the mixture MCI/MIT[3], which is 0.0015% (15 ppm). An SCL of 15 ppm for MIT (equal to the SCL of the mixture MCI/MI) is justified, based on existing evidence from epidemiological studies.

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[1] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_145.pdf
[2] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_178.pdf
[3] Annex VI of the CLP Regulation under the index number 613-167-00-5 : http://echa.europa.eu/nl/addressing-chemicals-of-concern/harmonised-classification-and-labelling/annex-vi-to-clp

SCCS comments to the individual parts of the CLH-report on MIT

I. Identified uses of MIT
p. 16: Identified uses are mentioned here: 'MIT is widely used preservative product type 6 (in-can) preservatives, 11 (preservatives for liquid-cooling and processing systems), 12 (slimicides) and 13 (metalworking-fluid preservatives) according to Annex V of Regulation (EU) No. 528/2012)'.

SCCS comment
The above represents uses of MIT as biocide (concentrates). Other preservative uses of MIT should also be mentioned (e.g. wet wipes for cleaning of surfaces, liquid soaps and other cosmetics).

II. Skin sensitisation section 4.6 of the report
Non-human information

In the proposal six animal tests are mentioned, which have been performed by the producers: 1 Buehler test, 2 Guinea Pig Maximization tests (GPMT), 1 Open Epicutaneous Test (OET) and 2 Local Lymph Node Assays (LLNA). Two tests from the open literature are mentioned as well. MIT was reported to be a weak sensitiser in a Guinea pig skin sensitisation test (Bruze et al, 1987) and a strong one in the LLNA (Basketter, et al., 2003A). The latter study supports the classification of MIT as a skin sensitiser 1A.

SCCS comment
The full study reports are not available, making it impossible to independently evaluate the studies. SCCS noticed that the result from one of the LLNA studies was inconsistent with the results from the other LLNA study and open literature. We have some specific comments regarding interpretation of the results from these animals studies (summarized in Appendix 1). SCCS would appreciate if these comments would be considered in the CLH proposal.

p. 40 Human information

Induction studies in humans

Six studies are mentioned using the HRIPT (Table 11b) p. 40 using induction doses from 0.01% to 0.06%. The challenge doses are not mentioned. Responses were seen to 0.01%, 0.04% and 0.05%, while the studies using 0.02%, 0.03% and 0.06% were negative. The tested substance was MIT 50% in propylene glycol.

Based on these data, as well as animal studies an SCL for skin sensitisation is set at 600 ppm (0.06%). It is argued in summary and discussion (4.6.1.3 p. 42) that the HRIPT is an exaggerated test, and a formulated product with MIT was used diluted in water, which may have given a vehicle effect, why 600 ppm (0.06%) and not 300 ppm (0.03%) is justified as concentration limit. At the same time it is stated 'that given the lack of dose-response in this study, it's suitability for defining an SCL is questionable. (p.42)'

SCCS comment
1. The same data as in Table 11b was part of the submission of data to the SCCS concerning MIT by Cosmetics Europe. The SCCS has concerns about the way these studies had been performed and therefore also questions the validity of the results (Opinion SCCS/1557/15 p. 13).
2. In the CLH document p. 42 it is mentioned that suitability of the studies for defining an SCL is questionable. It is therefore not appropriate to base a conclusion of SCL= 600 ppm (0.06%) from these studies. Responses at lower doses have not been taken into account. From the data presented (Table 11 b) it seems that even 100 ppm (0.01%) gives responses. This would fit with observations from humans, who have been exposed in real-life occupational scenarios.
3. There are no scientific reasons to specifically disregard the results from the lower dose groups, as has been done in the CLP report. It is not likely that skin irritation can explain the results. If irritation was a major driving factor of the results, one would not expect the top concentration 600 ppm (0.06%) to be negative.
4. In other human skin sensitisation induction models, skin irritation is deliberately performed to enhance induction (e.g. Human Maximization Test). This is done as these induction tests are not thought to be very sensitive in general and may miss out on important allergens (Menné et al 2002).
5. The SCCS considers the conduct of HRIPTs not ethical. CLP Article 7 (3) states: *'Human induction studies such as HRIPT or HMT must not be performed, although historical data may be used as weight of evidence for the sub-categorization.'*

Data from publications on dermatitis patients (Table 12 p. 40/41)

Seven studies are mentioned in Table 12 p. 40/41: these studies concern patients patch tested in Denmark, Germany, Austria and Switzerland, Finland, UK and Sweden. One study concerns Danish painters, who had been patch tested and one study is a repeated open study defining elicitation thresholds. In section 4.6.1.3 Summary and discussion of skin

sensitisation the previous SCCS opinions on MIT from 2014 is quoted. It is concluded p. 43 in the CLH report that: *'it has to be stressed that cosmetic products are intentionally applied to the skin and at higher doses, that is why setting the lower maximum concentration seems reasonable for cosmetic products'*.

The clinical data is evaluated in the following way (p.43): *'Skin sensitisation after exposure to MIT has been reported in several European countries in contact dermatitis patients. Some case reports on allergic reactions to MIT have also been published. From a scientific point of view the robustness of these data and their suitability for classification purposes is questioned, as many of the reports were not peer-reviewed, adequate reporting and presenting of data is lacking, and exposure was not sufficiently characterized.'*

SCCS comment

Clinical data and its role in classification

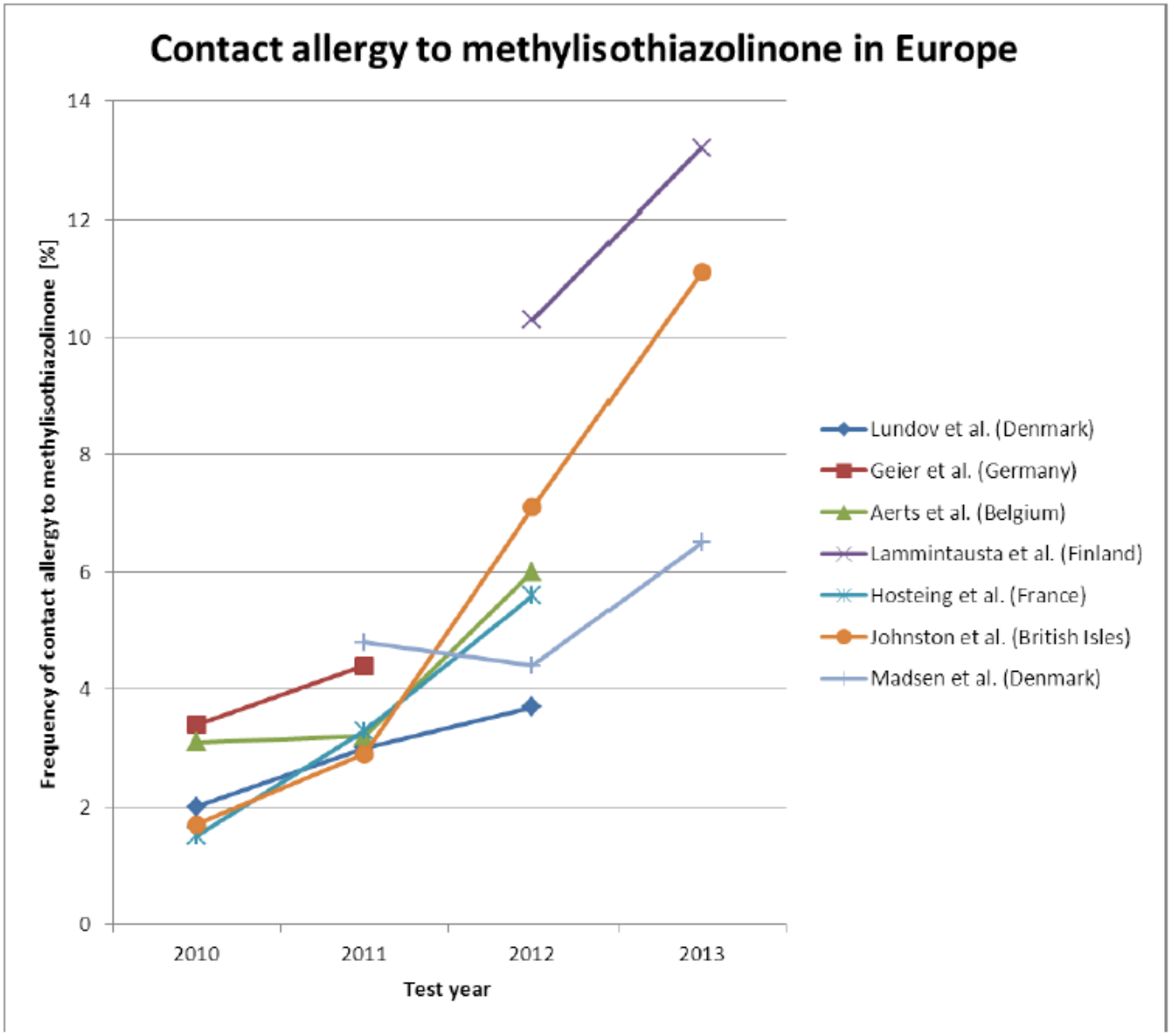
1. A Pubmed search of peer reviewed publications (http://www.ncbi.nlm.nih.gov/pubmed) performed 17th August 2015 showed 190 scientific papers from the search term: 'methylisothiazolinone contact allergy'; of the 122 in the past 5 years, 53 papers include the term 'occupational'. In the CLH report only 7 studies are mentioned.

2. Clinical data is part of the classification system and criteria; therefore it cannot be argued that none of up to 190 scientific papers is suitable for classification. Clinical data of the same standards and nature have been used as the basis of several legislations in EU e.g. the nickel directive, restrictions on chromium in cement and leather, where the clinical data has been used to set concentration limits. This should also be done for MIT under CLP.

Allergic contact dermatitis due to MIT

3. The first cases reported of MIT sensitisation concerned workers exposed to paint and glue (Thyssen et al. 2006; Isaksson et al. 2004). Later cases from consumer exposure to cosmetics were published (García-Gavín J et al. 2010). This has been followed by an unprecedented rapid increase in contact allergy to MIT as presented in SCCS opinions in 2013 and 2015 concerning MIT (see Figure below). The risk from exposure to cosmetics, stay-on and rinse-off are well recognized and described in the two opinions. A considerable proportion of cases are due to occupational exposures. Several occupations with an increased risk have been identified such as painters, beauticians and machine operators, mechanics, health care workers, hairdressers, café and restaurant workers and manufacturing workers (Uter et al. 2013; Schwensen et al. 2014; Vauhkala et al. 2015). Allergic reactions have in particular been related to detergents, metal working fluids, soluble oils, glues, paints, lacquers, concentrates, soaps for hand wash, industrial hand cleansers, barrier creams and wet wipes (Uter et al. 2013;Urwin et al. 2015; Vauhkala et al. 2015). Workers may develop severe allergic hand eczema, which may cause them to lose their job.

MIT has been shown to evaporate from fresh paint for at least 42 days (Lundov et al. 2014). Persons sensitised to MIT may react to the airborne exposures to MIT at the work place, at home or in public by severe allergic contact dermatitis at the exposed areas (Lundov et al. 2012). Cases with various respiratory symptoms to MIT have also been published (Alwan 2014).



Occupational exposures versus consumer exposure to cosmetics

4. Occupational exposures are –in general- not less intense than the use of cosmetics. Many cosmetic products are applied 1- 2 times á day, while at the work place the exposure may be continuous through a working day as for metal working fluid and detergents (Wassenius et al 1998; Jungbauer et al. 2004). In case of hand washing this may happen 5-10 times at home, but up to 50 times at the work place. Exposure to multiple products at the same time containing MIT may also happen in many occupations. The use of cosmetics is a deliberate choice, while at the work place there may not be a choice for the individual than using the products provided. Consumers can discontinue the use of a cosmetic product, which causes an allergic reaction without delay, while this is rarely possible at the work place. In many occupations gloves are not used at all or only sometimes, so exposure is directly on the skin.

Use concentrations of MIT

5. Painters have a high risk of sensitisation to MIT (Uter 2013; Mose 2012,) also cases due to paint among consumers have been reported (Lundov et al. 2010). In a European study wall paints (n=71) were randomly purchased in retail outlets in five European countries.

MIT was identified in 93.0% n=66 of the purchased paints. The MIT concentration ranged from 0.7 to 180.9 ppm, the majorities of products contained MI at 100 ppm (0.01%) or lower (Schwensen et al. 2015).
A search in the Danish Product Register Database, in which the composition of primarily hazardous chemical products for occupational use is registered, showed that 884 products were registered to contain MIT. The top three product types containing MIT were paint and vanishes, cleaning/washing agents and polishing agents. The mean concentrations ranged from 3 ppm (rinsing agents for dish washing machines) to 1.1% (11000 ppm in concentrates/biocides). Among 31 product categories, 23 (74%) had average concentrations of MIT below 100 ppm (0.01%) and 19 (61%) product categories had maximum concentrations of MIT below 300 ppm (0.03%) (Friis et al. 2014). MIT in up to 100 ppm in cosmetic products has caused many consumers to become sensitised.

Threshold responses

6. Spills or a few applications to high level exposures as from MIT containing biocide concentrates are known to cause induction of sensitisation (Thyssen et al. 2004), as it is also known for MCI/MI. However such exposures are unintended and rare compared to usual exposures to occupational and consumer products implicated in allergic contact dermatitis to MIT, such as detergents, metalworking fluids, paints etc. (see point 3). In a study from the Finnish Institute of Occupational Health one-quarter of patients with MIT and/or MCI/MIT contact allergy the sole identified exposure was via hand cleansers and liquid soaps (Vauhkala et al. 2015).
Cosmetics containing MIT at 100 ppm or lower are known to be causing sensitisation to an unprecedented level in Europe. Many occupational products contain similar levels (see point 5), but often with much more frequent/intense exposures. A SCL of 600 ppm (0.06%) is far above these levels. The suggested labeling limit of 60 ppm (0.006%) is also far above what is known about elicitation levels (Yazar et al. 2015; Lundov et al. 2011). The proposed SCL level for MIT will not provide any adequate protection from sensitisation or elicitation.

Material Safety Data Sheets

7. The Material Safety Data Sheets, which are the result of the classification including specific concentrations limits are crucial for the worker to be informed about risks and take appropriate measures; but also if an adverse reaction occurs, the MSDS has a pivotal role in detecting the causes of and preventing disease. In a recent investigation 33% of patients with contact allergy to MCI/MIT or MIT used products containing these preservatives without any mention of it in the MSDS or product declaration (Vauhkala et al. 2015). Similar deficits were detected in around 20% of MSDS from patients with occupational contact dermatitis concerning allergens including MIT, most often H317 was missing (Friis et al. 2014). This incomplete classification and labelling of MIT compromise prevention of a disabling disease among workers and consumers and the possibility of early detection and identification of cases. The current CLP requirement to label down to 1/10 of the GCL or SCL is not protective enough. Full ingredient labeling of classified skin sensitisers in chemical and occupational products is required for effective detection and prevention (Friis et al. 2014, Vauhkala et al. 2015).

MCI/MIT and MIT

8. MCI/MIT is classified as 1A sensitiser and with a SCL of 15 ppm (0.0015%). The MCI/MIT is a 3:1 mixture used since the 1980'ies as biocide both in consumer and occupational products. The frequency of allergic reactions to MCI/MIT was stable over many years around 2% of patch tested contact dermatitis patients (Svedman et al. 2012). But after the

introduction of MIT as a stand-alone biocide a rapid increase in contact allergy was seen not only to MIT, but also to the mixture MCI/MIT. This is due to MIT been present also in the mixture and chemical similarities between the substances (MCI and MIT), so that they may cross-react. This means that not only patients with MIT contact allergy may be affected by the exposures to MIT, but also those (to various extents) with MCI contact allergy. The substances should therefore be treated identically concerning SCLs from a scientific point of view.

III. Respiratory sensitisation section 4.6.2 of the report

In section 4.6.2.2 cases of airborne allergic contact dermatitis to MIT evaporating from paints are mentioned (Table 13.a). These cases do not concern respiratory sensitisation, but consequences of contact sensitisation to MIT. The information should be moved to the skin sensitisation section and included as evidence of the potential severe consequences of MIT contact allergy.

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Appendix 1. Specific SCCS comments on the animal studies on skin sensitisation

1. MIT is in the second GPMT study (A6.1.5/02) not a skin sensitiser at concentrations lower than 0.08 % a.i. GPMT is a semi-quantitative method that does not provide dose-response information. As such, it is not possible to set a concentration limt below which a substance is not a skin sensitiser. We recommend changing the conclusion of this study and state that

MIT is a sensitiser and remove the specific concentration in this column.
2. The same holds true for the conclusion on the third GPMT study (A 6.1.5-01). Please, remove the specific concentration of 1% in this column.
3. In the first LLNA study (A6.1.5/04) MIT was tested in 6 concentrations ranging from 0.15 – 1.8%. The results show a non-linear dose-response curve, which may be explained by the vehicle (water) used in this study. Water is not recommended as a vehicle in the LLNA, because it runs easily off the ears. This vehicle may impact the absorption of the test substance and the outcomes of the study.
In this LLNA, an SI value higher than 3 was reached at 1.35% MIT (SI value of 6.64). An EC3 value was not calculated. The conclusion drawn in Table 11a and on page 39 is not correct. It is stated that "In local lymph node assay concentrations of MIT greater than 0.76 % [152 µg MIT/ cm^2] gave positive results." At this concentration the SI of 3 is not yet reached. It would be better to derive an EC3 value that supports classification of a skin sensitiser 1A, rather than mentioning this specific concentration.
4. In the second LLNA (A6.1.5/05), MIT was tested up to 30% but did not induce a positive response. These results are in contrast to the first LLNA study and with the published LLNA study. An explanation for these inconsistent results was not provided.

ECHA note: An attachment was submitted with the comment above. As it contains the same content as the comment, it is not provided as a separate attachment.

Dossier Submitter's Response

Thank you for your extensive comments.
We agree that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

Response to comments:

I. Identified uses of MIT
For the purpose of this CLH dossier which presents an assessment of the hazardous properties of MIT and comparisons with classification criteria, providing additional data on uses and concentrations in this section is not required.

II. Skin sensitisation
Non-human information
According to your comments, Table 11 of the CLH report, summarising non-human data, should be corrected as follows.

Species/ Tested material	Method	Number of animals sensitised/total number of animals	Result	Reference
Guinea pig /Hartley, RH-24,573. (purity, 99.8% a.i.)	OECD 406, Skin sensitisation, Buehler GLP	Induction at 1000, 5000, 15,000 or 30,000 ppm MIT, equivalent to 0.1, 0.5, 1.5 and 3 % MIT Incidence of erythema after challenge with 1000 ppm MIT was 0/10, 0/10, 1/10, and 0/10, respectively. Incidence of erythema after challenge with 5000 ppm a.i. MIT was 0/10, 2/10, 1/10, and 2/10, respectively. Incidence of erythema after challenge at 15,000 ppm a.i. MIT was 1/10, 6/10, 3/10 and 5/10, respectively.	Sensitiser	A6.1.5/01 (Rohm and Haas)
Guinea pig /Hartley	OECD 406, Skin sensitisation,	Induction at 550 or 800 ppm (0.055 or 0.08 %) MIT Challenge of 500 ppm (0.05 %) MIT or 800 ppm	Not a sensitiser.	A6.1.5/02 (Rohm and

(purity 99.7% a.s.)	Magnusson-Kligman GLP	(0.08 %) MIT at 24 or 48h, no dermal reactions. Rechallenge phase: 4/20 animals induced at 550 ppm (0.055 %) a.i. exhibited a dermal reaction to the rechallenge application of 1000 ppm a.i. (0.1 %) 5/19 animals induced at 0.08 % a.i. responded to 0.1 % a.i.		Haas)
Guinea pig /Dunkin-Hartley, Acticide SR 3267, (purity 49 % a.i. in water)	OECD 406, Skin sensitisation, Magnusson-Klingmann GLP	First induction: 0.1 % intradermally. Second induction: 10 % topical application under occlusion for 48 hours. Challenge: 1 % topical application under occlusion (24 hours). Positive reaction was observed in 10/10 treated animals in 4/10 intensive erythema and swelling. In control animals no positive reaction was observed.	Sensitiser	A 6.1.5-01 (Thor GmbH)
Guinea pig /Hsd Poc:DH (SPF), 19.7 % MIT in water.	Skin sensitisation, Open Epicutaneous Method	For induction and challenge the same concentration of MIT in ethanol/aqua bidest. (40 % eth.) was applied. Doses used/positive skin reaction: -18 % 4/8 -1.5% 1/8 -0.6% 1/8 -0.4% 3/8 -0.25% 1/8 -0.15% 0/8 - control 1/8	Sensitiser	A6.1.5/03 (Rohm and Haas)
Mice/ CBA/J; 10.37 % MIT in water.	OECD 429, Local lymph node GLP	Stimulation index was: 2.08 at 0.15 % 2.40 at 0.45 % 2.23 at 0.76 % 6.64 at 1.35 % 4.73 at 1.57 % 6.62 at 1.8 % EC3=0.86 %	Sensitiser	A6.1.5/04 (Rohm and Haas)

In the second LLNA test (A6.1.5/05, Rohm and Haas) a MIT metabolite, NMMA (N-(Methyl) malonamic acid) found in rat metabolism study, was tested instead of the active substance MIT. This information was included by mistake and should be removed from the table.

Human data

When preparing the CLH report we were not aware of the SCCS/1557/15 comment regarding the validity of HRIPT studies with MIT, used to propose to SCL. According to the comment of the SCCS at lower doses of MIT, the induction might have happened but the challenge dose was not high enough to demonstrate that, since both, induction and challenge were performed with the same concentration of MIT.

We agree that based on the rising incidence of MIT sensitised individuals, sensitisation reactions observed after exposure to doses, much lower than 600 ppm, and the wide use of MIT in occupational and consumer products we agree that the SCL 0.06 % for MIT is not adequately protective for induction and elicitation of allergic skin reactions. In the CLH report some publications on MIT inducing/eliciting skin sensitisation were summarised, including the SCCS Opinion on MIT (March 2014).

We support your proposal that in MSDS full ingredient labeling of classified skin

sensitisers in chemical and occupational products is required for effective detection and prevention of skin allergies, resulting not only from MIT exposure, but also to CMIT exposure since cross reactivity of both was demonstrated in some publications.

III. We agree that the information on respiratory effects of MIT (section 4.6.2.2.-Table 13a) is moved to the skin sensitisation section and included as evidence of the potential severe consequences of MIT contact allergy following airborne exposure to MIT. Table 13 b should be included in section 4.6.1.2.

RAC's response

Thank you for the comprehensive analyses. RAC considers all the additional information to be of relevance to the setting of a specific concentration limit for the classification of MIT as a skin sensitiser.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Sweden	Institute of Environmental Medicine, Karolinska Institutet	Academic institution	5

Comment received

The Institute of Environmental Medicine (IMM) at Karolinska Institutet (KI) hereby responds to the open consultation regarding the proposal for harmonised classification and labelling of 2-methylisothiazol-3(2H)-one (MIT). IMM is a research department at KI and also a national institute in the area of environmental medicine and health risk assessment. Focus is on chemical, physical and life style factors within four major areas; epidemiology, toxicology, physiology and environmental and occupational medicine.

Comment on "2 Manufacture and uses"
The widespread use of MIT should be reviewed, including detailed information on product types and use concentrations. This is important background information since people are sensitised by the concentrations used today.

ECHA note: the following confidential attachment was provided with the comment above:

- *Yazar K., Lundov M.D., Faurschou A.,Matura M., Boman A., Johansen J.D. and Liden C., Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study.*

Dossier Submitter's Response

We agree that additional uses of MIT could be metioned in CLH MIT report. But based on the purpose of CLH dossier we do not agree with providing uses concentrations.

RAC's response

RAC concurs with the Dossier Submitter's response.

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2015	Norway		MemberState	6

Comment received

Norway would like to thank Slovenia for the proposal for harmonised classification and labeling of 2- methylisothiazol-3(2H)-one (MI(T)), CAS no. 2682-20-4.

Dossier Submitter's Response

Thank you.

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2015	Germany		MemberState	7

Comment received

Based on animal data, the dossier submitter proposed classification as Skin Sens. 1A, H317 (May cause an allergic skin reaction). This classification proposal is supported by the German CA.

However, based on newly available literature, it is suggested to propose a specific concentration limit of 0.001 % for MIT (see detailed comments below).

In the reference substance data set for 2-methylisothiazol-3(2H)-one the CAS name is missing and should be added.

In IUCLID section 1.2 two substance compositions are given (one from "Rohm and Haas" and one from "Thor GmbH"):

We like to mention, that although most of the impurities have a corresponding CAS entry and the CAS No. is stated in the particular reference substance data set, the CAS name is missing in some cases and should be added. For one of the impurities in the composition from "Rohm and Haas" only the IUPAC name and the reference substance name are stated. Both names do not describe the same substance. Because of the aspect that no further information on the identity of the impurity (like structural formula, molecular weight, SMILES etc.) is given, it cannot be concluded which name is the correct one. Please amend the given information and add the missing ones. The substance composition from "Thor" GmbH specifies a MIT technical concentrate mainly consisting of 50 % MIT in water (aqueous solution). In this composition water (ca. 50% w/w) is given as an additive. Although the MIT technical concentrate might be manufactured as described in the composition, according to the substance definition under REACH and CLP water cannot be seen as an additive in this case, because it does not stabilize the MIT. Therefore, the substance composition from "Thor GmbH" in section 1.2 of the IUCLID file should be amended.

In Part B, section 1.3, table 5 ("Summary of physic-chemical properties") of the CLH report it is stated that "Values for two sources of the substance are available and are listed". In order to understand why some of the values are differing slightly it might be useful to state the purities of the tested substances (as in the CAR for the active substance MIT).

In Part B, section 1.3, table 5 of the CLH report two values for the water solubility are given. For the first value (>1000 g/L) there are no information on pH and temperature. Please add the missing information.

In Part B, section 1.3, table 5 of the CLH report, amongst others, information on the "Partition coefficient n-octanol/water" is given. Since the purity/specification of the particular test items is not stated, it is not clear what the numbers in brackets ((1) and (2)) are referring to. A clarifying comment might be helpful.

In addition we have some editorial comments:

In section 1.2, concerning the "Specific concentration limits (SCL)" in Table 2 we like to

remark that the "A" is missing (Skin Sens. 1A).

In section 1.3, concerning the proposed Labelling we like to remark that in our opinion the "EUH071" should have its own heading i.e. "Suppl. Hazard statements".

Please check consistency of naming: HGPRT/HPRT and three-/two-generation study.

Please check consistency of unit "µg", occasionally written as "∝ g" (e.g. Table 9, column „Value RD50").

Please check consistent use of dose specification (mg Acticide SR 3267/kg bw/day respectively mg MIT/kg/bw/day) in Table 15d (Study A.6.8.1.-02 (Thor GmbH); column "Critical effects dams/foetuses") and corresponding text (p. 65, last passage).

Please check consistency of specified data in Table 15d (Study A.6.8.1-02 (Thor GmbH); column "Critical effects dams/foetuses") and corresponding text (p. 65, last passage): How many percent of foetuses in how many litters revealed unossified cervical vertebral bodies at 50 mg MIT/kg bw/day (respectively 100 mg Acticide SR 3267/kg bw/day) (78% in 21/21 litters or 76% in 20/21)?

Please check consistency of specified data in Table 13b (28 day study; column "Results") and corresponding text (4.7.1.1, passage 2): How many animals of which sex died at 71.2 mg MIT/kg bw/day (6, 5 or 4)?

Dossier Submitter's Response

Thank you for the support regarding the classification Skin sens. 1A, H317.
Proposal of SCL of 0.001 % was noted.

Thank you for (editiorial) comments.

IUCLID dossier:

- Section: Agree with your comments.

CLH report:

- Part B, Section 1.3; table 5: Agree with your comments.
- Section 1.2, Table 2 should read Specific concentration limits: Skin. Sens 1A; H317: SCL ≥ 0.06 %.
- Section 1.3, Labelling : heading Supplementary hazard statements should be stated in line above EUH071.
- In Table 14a in line 5 Gene mutation study (HPRT) in mammalian cells should be replaced by Gene mutation study (HGPRT) in mammalian cells
- unit "µg", occasionally written as "∝ g" is not visible on our computer. It might be due to different Word settings.

Text corresponding to the second rat teratogenicity study should read as follows (p.65 last paragraph): In the second rat study females were gavaged with 0, 67, 100 and 150 mg Acticide SR 3267/kg bw/day, corresponding to 0, 33.4, 50 and 75 mg MIT/kg bw/day from days 6 to 15 of gestation. No maternal deaths and clinical signs were observed in control and treated groups. Body weight gain of dams was significantly and dose-dependently

reduced in animals treated with 50 and 75 mg MIT/kg bw/day. In these groups food consumption decreased significantly. Body weight gain during the post-treatment period and total body weight gains during the pregnancy were similar in all experimental groups. There was no autopsy finding of reaction to the treatment in any dose groups.

- There were no significant differences in the number of the corpora lutea, implantations and viable foetuses among the examined groups and in the embryonic deaths and foetal death either. There were no significant or dose-related increases in pre- and post-implantation loss in any of the treated groups. Mean foetal body weights and placental weights were unaffected by maternal treatment with MIT. Foetal visceral examination revealed significant increase in number of minor anomaly, dilated cerebral ventricles, at 75 mg MIT/kg bw/day dose group.

- Number of the visceral variations decreased significantly in fetuses of mothers treated with 75 mg MIT/kg bw/day.Regarding skeletal anomalies the number of unossified cervical vertebral bodies was significantly increased at 50 mg/kg (76 % foetuses in 20/21 litters) and 75 mg/kg bw/day dose levels (72 % foetuses in 21/22 litters). Number of unossified metatarsals was significantly higher in the 75 mg/kg dose group (78 % foetuses in 21/22 litters) than in controls.

- Delay in ossification is probably related to decreased body weight gain of dams. In this study LOAEL 50 mg/kg bw/day and NOAEL 33.4 mg/kg bw/day were derived for developmental effects based on increased incidence of unossified cervical vertebral bodies. LOAEL 50 mg/kg bw/day and NOAEL 33.4 mg/kg bw/day were derived for maternal toxicity based on decreased body weight gain during gestation (Thor GmbH).

- Percent of foetuses with observed develpmental findings and the number of litters with such foetuses should be corrected as proposed (eg. 76 % foetuses in 20/21 litters). Corrections are included in the text above.
- In 28 days oral rat study 4 animals, treated with 71 mg/kg bw/day, died ; 1 male and 3 females.

RAC's response

RAC has taken into account the updaed information on the rat teratogenicity study provided by the Dossier Submitter in response to this comment.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	8

Comment received

In the justification (p 12), it is stated that 2-Methylisothiazol-3(2H)-one (MIT) is a biocidal active agent used as metal working-fluid preservative and for this reason is a subject to harmonized classification and labelling. While this is true, it has many more uses and the main concern is caused by its use as preservative in cosmetics and paints.

MSCA comments for Human Hazard only.
• NL asks to include the findings on sperm parameters from the repeated dose studies in the discussion on reproductive toxicity.
• NL agrees with classification as Cat. 1A for skin sensitisation, but disagrees with a specific concentration limit of 0.06%, as this limit is based on HRIPT studies that are not suitable for setting these limits. Clinical data that is not considered in this proposal provides evidence that 0.06% is not safe. As there have been numerous cases of contact allergies reported

after exposure to 0.01% MIT, the SCL should be 0.01% or possibly even lower.
• NL request a more thorough discussion on the choice not to classify for STOT RE, as severe effects were observed at relevant doses in several studies.

Dossier Submitter's Response

For the purpose of this CLH dossier which presents an assessment of the hazardous properties of MIT and comparisons with classification criteria, providing additional data on uses and concentrations in this section is not required.

Regarding the inclusion of sperm parameters into discussion on reproductive toxicity the following text should be included under section 4.11.4 of CLH report:

In one 90-days oral rat study changes in sperm parameters were observed in males exposed to MIT (Tables 1 and 2). Sperm motility was not affected by MIT treatment, except in recovery group, where some reduction was observed. This reduction was within historical control data (mean 93.4±2.17, max 96.6, min 86.5). Dose dependent reduction in the number of testicular sperm heads in testes was observed in animals treated with MIT. Although significantly reduced, the values are within historical control data range (mean 134.18±15.23, max 173.75, min 92.5). In two-generation study no effect on sperm count was observed after exposure to higher concentrations of MIT (60/40 mg/kg bw/day).
The reduction in epididymal sperm count is considered not to be biologically relevant taking into account no change in testes weight and no histopathological changes observed, a reduction within the historical data range (mean 1208.34±168.65, max 1592, min 805), absence of this effect in recovery group and in reproduction toxicity study where animals were exposed to higher doses of MIT. Statistically significant increase in per cent of abnormal sperm samples obtained from cauda epididymis in all treated groups (2.2, 2.55 and 2.67 % in animals treated with 7.5, 15 and 30 mg/kg bw/day, respectively) was reported compared to control group (0.75 %). In control recovery group 4.05 % sperms were morphologically abnormal and in high dose recovery group 4.95 %. Additionally, historical control data on sperm morphology in two-generation studies on Wistar rats indicate that in F0 generation 5.3 % of sperm heads were abnormal on average. Significant increase of abnormal sperm cells in this case could be due to low percentage of abnormal sperms in control group and is probably not treatment related.

Historical control data was submitted from the laboratory where the study was performed, for the strain tested in respective study, two-generation studies were used for derivation of historical control data and were performed withinh two years of the respective study. Animals were involved in the study for 120-135 days.

Table 1: Sperm parameters in MIT treated rats, 90 days study

Parameter	0 mg/kg bw/day		15 mg/kg bw/day		30 mg/kg bw/day		60 mg/kg bw/day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Motility count (%)	93.0	1.59	92.5	1.47	92.6	0.77	92.5	1.21
Testicular sperm head count (millions/g)	130.625	8.990	121.938↓	5.594	114.75↓↓	5.865	106.458↓↓	7.844
Epididymal sperm count (millions/g)	1355.35	90.98	1371.90	87.91	1438.30	172.52	1371.17	148.66
Abnormal sperm (%)	0.67	0.66	2.15↑	1.29	2.35↑↑	1.25	2.80↑↑	1.09

↓ - significantly lower than control (p≤0.05), ↓↓ - significantly lower than control (p≤0.01),
↑- significantly higher than control (p≤0.05), ↑↑ - significantly higher than control (p≤0.01)

Table 2: Sperm parameters in 14 days recovery groups of MIT treated rats, 90 days study

Parameter	0 mg/kg bw/day		15 mg/kg bw/day	
	Mean	SD	Mean	SD
Motility count (%)	92,9	0,77	91,3↓	1,68
Testicular sperm head count (millions/g)	120,875	10,401	133,688	26,320
Epididymal sperm count (millions/g)	1345,80	40,72	1335,85	67,87
Abnormal sperm (%)	4,05	1,46	4,95	1,19

Thank you for supporting the proposed classification Skin sens. 1A, H317. Considering the rising number of studies reporting increasing incidence of confirmed MIT sensitised individuals, skin sensitising reactions to MIT at doses below 600 ppm and wide use of MIT in industrial and consumer products the weight evidence shows that 0.06 % concentration of MIT is not the satisfactory specific concentration limit for classification of MIT as Skin Sens. 1A, H317 to protect individuals from adverse health effects.
We agree with the proposal of a SCL lower than 100 ppm. See also response to comment 1.

According to our opinion the classification of MIT as STOT RE 2 is not justified.
In 28-days oral rat study the animals of both sexes treated with high dose of MIT, 71 mg/kg bw/day, were lethargic during week 3 and 4. At this dose 4 animals died, 1 male and 3 females, and decreased body weight and food consumption were observed in males, while no reduction of these paraters was observed in females. Another oral repeated dose study was performed in rats. Animals were exposed to comparable dose of MIT, 66 mg/kg bw/day, for longer period (90 days), but no mortalities were reported, only slight reduction of body weight, food and water consumption.

One of the criteria for classification of a substance as STOT RE 2 is consistent and identifiable toxic effect in humans or experimental animals. Since mortalities observed in 28-days oral rat study were not seen in 90 days oral study, conducted with similar dose of MIT this criteria is not fulfilled. Longer exposure would be expected to result in more severe effects. According to criteria for classification STOT RE 2 clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity do not fulfil the criteria for classification STOT RE 2. Since only slightly reduced body weight, food and water consumption were observed in 90-days rat study, the classification of MIT as STOT RE 2 is not warranted.

RAC's response

Thank you for the rationale supporting a specific concentration limit for skin sensitisation of 0.01% or lower. RAC has taken into account the updated information on reproductive toxicity and the modified assessment of the STOT RE endpoint provided by the Dossier Submitter in response to this comment.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2015	United Kingdom	Not applicable	Individual	9

Comment received

I was diagnosed with skin sensitisation and allergy to MI/MCI in November 2014 having

suffered for almost 2 years with symptoms. This chemical is now so widely used that avoidance (being the best/recommended solution) is practically impossible. I have attempted to find products without MI ror use in my home and personal use. However, I cannot limit this to public areas. I no longer use any products on my skin/hair daily cleaning and so my allergy is now as a result of airbourne contact from paints, aerosols, washing powders and softners, cleaning products, air freshners etc. I have attached an image of my reaction to this chemical and I am happy for it to be used publicly. In order to remain safe from hives, rashes, extreme itching, angiodema and anaphylasis I am reduced to living in a bubble and using steroids & full dose antihistamine for the rest of my life.

ECHA note:
An attachment (image) was provided with the comment above.

Dossier Submitter's Response

Thank you for your comment.

RAC's response

RAC notes the seriousness of the health hazard posed by MIT and thanks the individual for sharing their experience. It is hoped that the outcome of this regulatory initiative will help to reduce risks for you and others in society in the future.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Germany	German Contact Dermatitis Research Group(Deutsche Kontaktallergie-Gruppe; DKG)	Scientific body	10

Comment received

Comment on dossiers proposing harmonised classification and labelling of substance: 2-methylisothiazol-3(2H)-one.

Against the background of our scientific data (as outline in attachemnt), hereby, we would like to inform the European chemicals agency that the MI threshold concentration of 0.06% (600 ppm) as proposed concentration limit for labelling is not evidence based and does not reflect the state of current scientific knowledge. It is definitely not low enough to protect consumers neither from skin sensitisation nor elicitation of allergic contact dermatitis and derails necessary exposure assessment.

ECHA note: The following attachment was provided with the comment above:

Statement of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe; DKG) concerning concentration limits for labelling of 2-methylisothiazol-3(2H)-one (MIT) in cosmetics and consumer products.

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
Proposal for SCL for skin sensitisation markedly below 50 ppm was noted, based on continuous increase of sensitisation to MIT (patch test at 500 ppm in aqua), from 2.0 % in 2009 to 7.2 % in 2013 and 2014 and study results of ROAT test performed to determine the elicitation threshold for MIT whre 52.5 % reacted to 200 ppm and 47.5 % reacted to 50 and 100 ppm.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for

MIT.
RAC's response
Thank you for the rationale supporting a lower specific concentration limit for skin sensitisation classification than that proposed initially by the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Finland		MemberState	11
Comment received				
Please, find the Finnish CA comments on HH endpoints: *ECHA note: Please refer to comments number 22, 25, 40 and 42*				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2015	Germany	Not applicable	Individual	12
Comment received				
As a victim of MI and MCI allergies, I would like to give comments to this chemical. *ECHA note: Please refer to comment 42*				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015		Astma-Allergi Denmark	National NGO	13
Comment received				
Statement from the Danish Asthma-Allergy Association The following statement is being issued by Asthma-Allergy Denmark, a democratic patient organization working with knowledge and activities that are aimed at people with allergies and hypersensitivity diseases such as asthma, hay fever and eczema. Asthma-Allergy Denmark offer advice for allergic people, carrying out projects in partnership with public and private actors. Asthma and Allergy Denmark are teaching children, adolescents and adults in allergy, allergic diseases and how everyday life with allergies can be managed. Asthma-Allergy Denmarks aim is primary prevention of allergy elicitation and sees this as an essential task of consumer safety and health. Today it is acknowledged by both industry and scientists that MIT due to the increased use and higher concentrations during the last decade has led to an almost epidemic increase of contact allergy to MIT in consumers across Europe. Once a person is sensitised it will lead to				

severe consequences including low and stressful quality of life. Not only due to job-loss but also due to the constant risk everyday of getting allergic reactions just by using common products such as soap. Another example could be a doctor's visit where ultrasound examination is impossible due to MIT-containing gel. Furthermore just breathing when entering a newly painted building can lead to eliciting allergy reaction since MIT can be found in the air long after painting a room with paint containing MIT.

Various products such as shampoo, lotion, liquid soaps, wet wipes, hand cleansers, detergents, skin care products, paints, metal-working fluids can contain MIT or MCIT/MIT. It has to be stressed that Asthma-Allergy Denmark finds it as no valid argument to use higher MIT concentrations in e.g. paint than in cosmetic products because cosmetics are intentionally applied to the skin. There is in general also a risk of direct skin contact to other products besides cosmetics such as e.g. paint. During a common painting process skin contact can happen and the contact will most probably last for a period due to the difficulties of washing. In addition it is well known from multiple case reports that allergic reactions can occur via airborne exposure to vapours of drying paint containing MIT. Some of which has been of very severe character in terms of allergic contact dermatitis of exposed skin (mostly face, hands and arms).

A "use test study" mentioned in the opinion and conducted by the CE in May, 2015 examined the use of common soap preserved with 50 or 100 ppm MIT five times a day. The study showed elicited allergic reactions in all or almost all sensitised patients. SCCS's expresses that the current use of 50-100 ppm in cosmetic products can play a potential role in the induction of contact allergy to MI.

In the latest opinion from SCCS (2015) a limit of 15 ppm (0,0015%) is suggested as safe concentration for cosmetic "Rinse off" products. SCCS expresses that this concentration is chosen for safety reasons based on that no higher concentration seems to be safe for either induction or elicitation. That means that the concentration is set regardless the lack of valid data to determine a No Effect Level. The lack of valid data to determine a No effect level raises concern weather a limit of 15 ppm as safe concentration in Rinse Off products is adequate.

To assure primary prevention of contact allergy assigning adequate risk phrase and labeling are crucial. It is of highest importance that this is viewed in the context of the high prevalence of MIT sensitisation and with the increase in MIT contact allergy that can be expected in the future. In primary prevention it is essential to be able to avoid products containing MIT or MICT/MIT and that is only possible if the substances are required mentioned in safety data sheets and product declarations/package. Hence the labelling limit should be set to 0%.

The above statement enlightens the current situation and concern we experience in Asthma-Allergy Denmark and it is essential to acknowledge before justifying safe threshold concentration limits for worker and consumer safety.

Thorkil Kjær
Director Asthma-Allergy Denmark

Dossier Submitter's Response

Thank you for the comment. We agree that the primary prevention of exposure to MIT could be achieved by labelling of all products containing any concentration of MIT, alone or in mixture. Therefore we support the proposal that all industrial and consumer products are labelled with EUH208: "Contains 2-methylisothiazol-3(2H)-one. May produce an allergic reaction."

RAC's response
RAC notes the additional level of concern for already sensitised people and the proposal to set a limit of 0% for the labelling phrase EUH208. The rationale for this position is clear.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	14

Comment received
CLH-Report, Chapter 4.10 p. 58 Carcinogenicity We do agree with the conclusion that MIT is not carcinogenic and no classification is required. However, we are of the opinion that the presentation within the CLH-report is to brief and does not reflect on the data basis available to come to this conclusion. Chronic and carcinogenic toxicity of MIT has not been tested. However, two chronic toxicity/carcinogenicity studies performed with the mixture of C(M)IT/MIT (3:1) are available. Within the CLH-report those studies are not referenced. However, the CAR Doc IIA (of June 2014, Chapter 3.9.1) concludes as followed: "Chronic toxicity of MIT has not been tested. Waiving of chronic toxicity study is justified by toxic profile of MIT in subchronic and reproductive toxicity studies, by negative results of genotoxicity studies and by submitting two chronic toxicity/carcinogenicity studies performed with the mixture of CMIT/MIT (3:1)." See also confidential attachment 1. *ECHA note: The following <u>confidential</u> attachment was provided with the comment above:* Confidential attachment submitted by Thor GmbH on 27.08.2015 relating to the carcinogenicity endpoint

Dossier Submitter's Response
The information regarding carcinogenicity/chronic toxicity studes of MIT in combination with CMIT was included in the first draft of the CLH Report for MIT that was submitted to ECHA. This information was later removed from the CLH dossier since ECHA commended that studies performed with CMIT/MIT (3:1) may have met data requirements in the biocides programme, but they are not relevant to the classification of MIT itself and should be deleted from the CLH report or otherwise to provide clear justification on the similarity. If there are no data on MIT for a particular endpoint, it is sufficient simply to state this fact (no data available). That is the reason why this information is not presented in the CLH dossier. However, when MIT was evaluated under Biocidal Regulation it was concluded not to be carcinogenic based on the available information.

RAC's response
Noted; RAC agrees with the response provided by the Dossier Submitter.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-METHYLISOTHIAZOL-3(2H)-ONE (ISO)

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	15
Comment received				
CLH-Report, Chapter 4.9 p. 52 f Mutagenicity Considering the results of all available in vitro and in vivo data, addressing the endpoint mutagenicity, we do agree with the conclusion that MIT is not mutagenic.				
Dossier Submitter's Response				
Agreed.				
RAC's response				
Noted; RAC agrees with the response provided by the Dossier Submitter.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	16
Comment received				
CLH-Report, Chapter 4.11 p. 58 f Reproduction Considering the data available, we do agree with the conclusion, no developmental effects were observed either in rats or rabbits treated with MIT and no effects on fertility and sexual function were observed. We do agree with the overall conclusion that for MIT no classification and labelling is required, in respect of reproductive toxicity.				
Dossier Submitter's Response				
Agreed.				
RAC's response				
Noted; RAC agrees with the response provided by the Dossier Submitter.				

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	17
Comment received				
Changes in sperm parameters were observed in a repeated dose study on p.50 (reduced sperm motility and sperm heads). Although the changes were within historical control range, we request these findings are included in the discussion on reproductive toxicity (fertility).				
Dossier Submitter's Response				
Please see response to comment 8.				
RAC's response				
Please see response to comment 8.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	18
Comment received				
CLH-Report, Chapter 4.6.2 p. 45 f Respiratory sensitisation Considering all available data suitable for classification, we do agree with the conclusion drawn: MIT does not fulfil the criteria for respiratory sensitisation.				
Dossier Submitter's Response				
Agreed.				
RAC's response				
Noted; RAC considers that the data are not sufficient for classification.				

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2015	Switzerland	Dow Europe GmbH	Company-Manufacturer	19
Comment received				
The dossier discussion on respiratory sensitisation describes cases of airborne contact dermatitis that are not relevant for respiratory sensitisation but should be discussed in the context of dermal sensitisation. Reports in the dossier specifically describe dermal sensitisation cases as a result of deposition of MIT on the skin from the surrounding air, the implication being that MIT is a potent dermal sensitiser that can cause outbreaks of allergic contact dermatitis in already induced persons. See attachment *ECHA note: The following attachment was provided with the comment above:* - *Dow comments to MIT CLH proposal*				
Dossier Submitter's Response				
Agreed. The information on respiratory effects of MIT (section 4.6.2.2.-Table 13a) should be moved to the skin sensitisation section and included as evidence of the potential severe consequences of MIT contact allergy following airborne exposure to MIT. Therefore Table 13b should be included in section 4.6.1.2.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	20
Comment received				
CLH-Report, Chapter 4.2.1.1 p. 29 Oral Considering all available data suitable for classification, we do agree with the proposed classification for acute oral. Following the cut off values in the most recent guidance on application of CLP criteria, MIT would be Cat. 3 for the oral acute toxicity. CLH-Report, Chapter 4.2.1.2 p. 29 f Inhalation				

Considering all available data suitable for classification, we do agree with the proposed classification for acute inhalation. Following the cut off values in the most recent guidance on application of CLP criteria, MIT would be Cat. 2 for the inhalation acute toxicity.
We question the relevance of data obtained by means of an aerosol in view of the low vapor pressure of the substance and of the intended and reasonably expected conditions of handling and use of the substance.
There is an unnecessary, superfluous and detrimental inflation of labelling with GHS06 due to anticipation of artificially maximized aerosol exposure.

CLH-Report, Chapter 4.2.1.3. page 30/31
Dermal
We do not agree with the proposed classification for acute dermal toxicity.

p. 31. "The results of two reliable acute dermal toxicity studies differ, but based on study summaries and study reports there is no clear reason for such difference. However, the proposal for classification of MIT regarding acute dermal toxicity is based on more conservative study."

The results of the two studies submitted differ because two different states of aggregation of the active substance were tested in the two different studies.

The Dow data (LD50 = 242 mg MIT/kg bw; Cat 3) have been measured with the solid/neat substance (97.5%) wetted with vehicle, but the Thor data (LD50 > 2000 mg MIT/kg bw; Cat 5) were obtained with a technical watery dissolution (50% ai).

We do suggest a "split entry classification" to recognize the two different conditions of aggregation of MIT which lead to different results in respect of dermal toxicity.

We question the relevance of data obtained with wetted powder versus dissolved active substance for classification of the substance and downstream products.

Dossier Submitter's Response

Your support for classification in cat. Acute Tox.2 for oral toxicity was noted.

In acute inhalation toxicity studies severe effects were observed, including mortalities, that could result from corrosive properties of MIT. Based on findings of three acute inhalation toxicity studies with MIT according to our opinion the classification Acute Tox.2 is justified in regard to acute inhalation toxicity.

A split entry classification is according to our knowledge not possible. As already mentioned both acute dermal toxicity studies were performed according to the valid guidelines and GLP. Since both studies were performed with MIT in water, in one case MIT moisted with water and in second diluted in water, we assume that was not the reason for difference in study outcomes. Therefore we still support the classification into Acute tox. 3 category regarding acute dermal toxicity of MIT.

RAC's response

RAC notes the comments provided, but agrees with the Dossier Submitter on the dermal toxicity classification.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-METHYLISOTHIAZOL-3(2H)-ONE (ISO)

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2015	Switzerland	Dow Europe GmbH	Company-Manufacturer	21
Comment received				
We agree with the DS proposal that classification of MIT technical grade (>95%) for acute oral toxicity (Cat. 3) and acute dermal toxicity (Cat. 3) is appropriate. We question the need for classification for acute inhalation toxicity. At rtp, MIT is a solid. As a result the potential for inhalation exposure to the technical material is considered negligible. We question the relevance of the acute inhalation classification for MIT given the effects observed in the acute inhalation study were primarily due to the irritating/corrosive nature of the test material. See attachment. *ECHA note: The following attachment was provided with the comment above:* Dow comments to MIT CLH proposal				
Dossier Submitter's Response				
Please see response to comment 20, part referring to the classification regarding acute inhalation toxicity.				
RAC's response				
RAC notes the comment but agrees with the Dossier Submitter. The inhalation toxicity of MIT is predictable given its corrosive nature.				

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Finland		MemberState	22
Comment received				
Acute toxicity (oral, dermal, inhalation: The Finnish CA agrees with the proposed acute toxicity classifications according to Regulation (EC) No 1272/2008 (CLP) for 2-methylisothiazol-3(2H)-one: Acute Tox. 3 (oral), H301; Acute Tox. 3 (dermal), H311; Acute Tox. 2 (inhalation), H330.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	23
Comment received				
For the first dermal toxicity study, with the LD50 of 242 mg/kg, it is first stated that this is the LD50 for male rats (p. 28 and 30). On p.31 it stated that this value was measured in females.				
Dossier Submitter's Response				
The LD_{50} of 242 mg/kg bw was determined in male rats. On p. 31 the second passage of section 4.2.4 should state: Acute dermal toxicity: MIT shall be classified as Acute Tox. 3; H311 (Toxic in contact with skin) on the bases of the lowest LD_{50} 242 mg MIT/kg bw (male rat), because this LD_{50} is within the limits 200 mg/kg < $LD_{50} \leq$ 1000 mg/kg.				

RAC's response
The clarification is noted.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	24
Comment received				
CLH-Report, Chapter 4.5 p. 35 f Considering all available data suitable for classification, we do agree with the proposed classification for skin corrosion, category 1B H314 being applied.				
Dossier Submitter's Response				
Thank you for support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Finland		MemberState	25
Comment received				
Skin corrosion / irritation: The Finnish CA is of the view that the data presented in the CLH report is not sufficient for classification of 2-methylisothiazol-3(2H)-one as Skin Corr. 1B; H314 according to CLP Regulation. Although erythema is noted still after 14 days observation period following 1 hour exposure, no clear corrosive responses indicating destruction of skin tissue (e.g. visible necrosis) have been described in the in vivo studies presented. Thus, notwithstanding that the erythema was not reversible and its score values remained high to the end of the observation period, it should be considered to classify 2-methylisothiazol-3(2H)-one as Skin Irrit. 2; H315.				
Dossier Submitter's Response				
In one submitted skin irritation study (A6.1.4/01 Rohm and Haas) where rabbits were exposed to MIT for 1 h or 4 hrs under semi-occluded dressing the following skin findings and skin irritation scores were observed (Tables 1-). Table 1: Skin irritation scores after 1 h exposure to MIT				

Parameter	Time after patch removal				
	1 h	24 hrs	48 hrs	72 hrs	7 days
Erythema	3 b	4 c	4 c	4 c,d	4 e
Edema	4 a	4 a	4 a	4 a	0

a – pocketing edema, b- darkened areas, c-blackened areas, d- blanching, e- concave eschar

Table 2: Skin irritation scores after 4 hrs exposure to MIT

Parameter	Time after patch removal					
	1 h	24 hrs	48 hrs	72 hrs	7 days	14 days
Erythema	4 b	4 b	4 b,c	4 b,c	4 b,c	4 d
Edema	4 a	4 a	4 a	4 a	4 a	0

a – pocketing edema, b- blackened areas, c- blanching, d- concave eschar

In the second skin irritation study (A6.1.4-01 (Thor)) findings reported in Table 3 were observed.

Table 3: Skin irritation scores after 4 hrs exposure to MIT

Animal No.	1 hour		24 hours		48 hours		72 hours		7 days		10 days		14 days	
	Ery	Oed	Ery	Oed	Ery	Oed	Ery	Oed	Ery	Oed	Ery	Oed	Ery	Oed
1	1	1	2	1	2	1	2	1	4	*	4	*	4	*
2	3	0	3	0	3	0	3	0	4	*	4	*	4	*
3	1	3	1	2	1	1	1	1	4	*	4	*	4	*

* = not evaluated due to eschar formation

Based on these findings we consider the classification Skin Corr. 1 B, H314 justified for MIT.

In addition, in acute dermal toxicity study dermal effects were observed on day one and continued to be observed throught the study duration (14 days). These effects included blanching, edema, darkened areas, eschar formation, sloughing, scrabbed areas and desiccation.

RAC's response

The irreversibility of the erythema, together with the observation of blanching and concave eschar in the first rabbit study, are collectively considered to be evidence of corrosivity. Since these effects occurred in conjunction following 1 hour exposure, RAC agrees with the DS that MIT meets the criteria for classification as Skin Corr. 1B; H314 (Corrosive in >1 of 3 animals following exposure > 3 minutes - ≤ 1 hour, with an observation period of ≤ 14 days). The results of the *in vitro* human epidermal construct study are considered to support this classification.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2015	United Kingdom	Not applicable	Individual	26

Comment received

Hives, rashes, itching, blistering, angiodema, urticaria, eczemous reaction

ECHA note:

An attachment (image) was provided with the comment above

Dossier Submitter's Response

Noted.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	27

Comment received

In the part on sensitisation on p.40, an occupational accident is described, in which a worker suffered from blistering and reddening of the skin after exposure to MIT. As this seems an acute effect, rather than an allergic reaction, this incidence should be included in the discussion on irritation/corrosion.

On p.36, the erythema score for the 3-minute exposure is erroneously given as 0.1.

The irreversibility of erythema is not determinative for classification as corrosive but only for category 2. Please provide information whether additional effects indicating corrosivity were

observed in the skin irritation corrosion studies, which could justify classification as corrosive. In addition, the local effects in the acute dermal study could be used to support the classification as corrosive.

Dossier Submitter's Response

Agreed. The following paragraph should be moved into section 4.5.2 on page 36:

An accident with MIT was reported when one of the workers in Rohm and Haas was exposed to the substance. In this case blistening and reddening of skin were the signs of exposure. Over the years of manufacturing MIT no worker has experienced continuing skin problems and none has had to be transferred to other duties due to exposure to chemicals.

The text on p.36, section 4.5.3 should be corrected as follows:

MIT is considered to be corrosive to skin and eyes (eye irritation potential of MIT was not tested since MIT is corrosive to the skin) based on the corrosive effects observed in rabbits exposed to MIT for 3 minutes (6 animals average erythema score 1.0, edema score: 0.4, erythema persisted for 7 days), 1 hour and 4 hours (erythema and edema score 4.0, erythema irreversible after 7 days) (Doc IIA, A6.1.4/01) and corrosiveness in human skin epidermal construct (after 60 minutes exposure to 51.5 % MIT reduction of cell viability to 13.6 %) (Doc IIA, A6.1.4/02).

Regarding classification Skin Corr. 1B, please see response to comment 25.

RAC's response

Please refer to response to comment 25.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	United Kingdom	Confidential	Company-Manufacturer	28

Comment received

The use of MIT in our product types has resulted in extremely rare amount of skin reactions. We therefore feel that the generic concentration limit of 0.1% is adequate in our experience for out products.

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response

RAC notes the comment, but considers other data supporting a specific concentration limit to be overwhelming.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	France		MemberState	29

Comment received

Specific concentration limit for skin sensitisation:

First, please update the CLH report with the recent data based on the SCCS opinion dated of June 2015 and also with the version of 2013. Indeed, several studies show results which do not support your proposal of specific concentration limit (please see the references from the SCCS opinion interesting to add at the end of the comment). For example, from the recent SCCS opinion, the publication of Yasar K & al., 2015 and cosmetovigilance data should be added in the CLH report. The opinion shows that either 100 ppm or 50 ppm MIT (for elicitation or induction) are not safe for consumers using rinse-off products. Therefore, the proposed specific concentration limit for skin sensitisation of 0.06% (corresponding to 600 ppm) appears to be too high to protect the population.

Moreover, this scientific rationale behinf this value of 0.06% is questionable. Indeed, eCA mentioned a lack of dose-response relationship in the study on which the value is based (Politano VT and Api AM, 2008). There are also positive responses noted below this value of 0.06%.
In parallel, the choice of challenge concentrations is doubtful; the maximal concentration that can be tolerated without causing skin irritation should be used for demonstrations of sensitisation. In this study, the lower challenge concentration of 200 ppm may have been not sufficient to reveal induction. Consequently, the choice of this value of 0.06% is difficult to justify.

In addition, for another strong sensitiser, in the CLH report of C(M)IT/MIT a specific concentration limit for skin sensitisation of 15 ppm (corresponding to 0.0015%) is proposed by France based on the SCCS opinion. It is written in the CLH report of C(M)IT/MIT that information leading to ascertain the most optimal concentration to detect cases of sensitisation exists. However no new information is available to challenge the classification threshold value of 15 ppm set during the Commission Working Group on the Classification and Labeling of Dangerous Substances in 2000 in order to avoid the induction of skin sensitisation during exposure with product containing C(M)IT/MIT. The most relevant data leading to a modification of this threshold value have already been reviewed during this meeting. A concentration of C(M)IT/MIT in product not exceeding 15 ppm do not lead to a risk of primary sensitisation and elicitation is also not expected at this concentration.

Finally, a dramatic increase in the incidence of cases of sensitisation due to the use of MIT has recently been observed observed. An increase in the incidence of sensitisation due to the use of isothiazolinones (in global) may also be expected considering the potential pattern of cross-reactivity observed with these substances. This deserves serious attention and management measures should be taken to avoid such health issues.

In conclusion, based on these arguments and in order to harmonize the specific concentration limits with another isothiazolinone C(M)IT/MIT, FR has the opinion that a classification limit for skin sensitisation of 15 ppm should be applied for MIT.

References from the SCCS opinion interesting to add in the CLH report:
-Basketter D A, Gilmour N J, Wright Z M, et al. 2003
-Rohm & Haas, (2003) Report 06R-l002. Methylisothiazolinone: local lymph node assay (methylisothiazolinone 10.37% active ingredient). Unpublished data submitted by Rohm & Haas and referred to in Burnett, CL, Bergfeld WF, Belsito DV et al. 2010
-Roberts DW, Patlewicz G, Kern PS, et al. 2007
-Estrada E, Patlewicz G, Chamberlain M et al. 2003
-Roberts DW 2013
-Lundov MD, Zachariae C and Johansen JD. 2011

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.

The SCCS opinion on MIT from 2013 (revised March 2014) is already summarised in the CLH dossier.
The following text regarding the SCCS Opinion (June 2015) should be included under section 6.4.1.3:
In June 2015 the *Scientific Committee on Consumer Safety (SCCS) opinion on Methylisothiazolinone (P94), Submission III (Sensitisation only)* was prepared concerning the safety of MIT in rinse-off and hair leave on products. For the preparation of the opinion data review of SCCNFP opinion on MIT from 2003 to 2004, skin allergy assessment and the quantitative risk assessment, compilation of cosmeto-vigilance data related to cosmetic products containing MIT and the assessment of impact on the risk of induction of skin sensitisation from aggregated exposure arising from use of rinse-off cosmetic products containing 100 ppm MIT were submitted. The opinion concluded that the information provided does not support the safe use of MIT as a preservative in rinse-off cosmetic products up to a concentration limit of 100 ppm from the view of induction of contact allergy. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the point of view of induction of contact allergy. The information provided does not support the safe use of MIT as a preservative in leave-on hair cosmetic products up to a concentration limit of 100 ppm from the point of view of induction of contact allergy. The concerns and opinions raised in SCCS Opinion SCCS/1521/13 (12 December 2013 with revision 27 March 2014) remain. The results of the recent Scandinavian study do not support safety of MIT in rinse-off products at either 100 ppm or at 50 ppm for elicitation or induction.

The publication of Yazar should be included in the additional raw in Table 12. In addition, data on ROAT test, published by Lundov 2011, should be corrected in the respective Table as given in the Table below.

<table>
<tr><th>Study type</th><th>Subject and dose tested</th><th>Positive response to MIT</th><th>Reference</th></tr>
<tr><td>Repeated open application test (ROAT)</td><td>19 MIT positive individuals
ROAT: 50 and 100 ppm MIT applied in liquid hand soap, 5×/day, until positive reaction was observed or day 21.</td><td>Endpoint: Elicitation
ROAT:<table><tr><td>Dose (ppm)</td><td>Reaction</td></tr><tr><td>100</td><td>10/10</td></tr><tr><td>50</td><td>7/9</td></tr></table></td><td>Yazar e tal., 2015, British Journal of Dermatology, 173:115-122.</td></tr>
<tr><td>Repeated open application test (ROAT) and patch test were performed</td><td>11 patients sensitised to MIT
Patch test: 12 concentrations: 0.2, 0.1, 0.05, 0.03, 0.015, 0.01, 0.005, 0.0015, 0.0007, 0.0005, 0.00035, 0.000035% MIT, twice daily.</td><td>Endpoint: Elicitation
Patch test:<table><tr><td>Dose (%)</td><td>Reaction</td></tr><tr><td>0.2</td><td>10/11</td></tr><tr><td>0.1</td><td>10/11</td></tr><tr><td>0.05</td><td>10/11</td></tr><tr><td>0.03</td><td>10/11</td></tr><tr><td>0.015</td><td>8/11</td></tr><tr><td>0.01</td><td>7/11</td></tr></table></td><td>Lundov et al., 2011, Contact Dermatitis, 64, 330–336</td></tr>
</table>

	ROAT: 0.0007, 0.00035, 0.000035% MIT. The use of cream protected with MIT was mimiced	<table><tr><td>0.005</td><td>6/11</td></tr><tr><td>0.0015</td><td>0</td></tr><tr><td>0.0007</td><td>0</td></tr><tr><td>0.00035</td><td>0</td></tr><tr><td>0.00035</td><td>0</td></tr></table> ROAT: <table><tr><td>Dose (ppm)</td><td>Reaction</td></tr><tr><td>100</td><td>7/11</td></tr><tr><td>50</td><td>7/11</td></tr><tr><td>5</td><td>2/11</td></tr></table>		In section 4.6.1.1

. the following corrections should be made:

- Table 11a, Line 5: LLNA in CBA/J mice: calculated EC3 is 0.86 %. This is the study by Rohm and Haas that you advice to include in the CLH report.

Regarding further references of interest to be included in the CLH report:

- LLNA study of several preservatives performed by Basketter, Gilmour, Wright et al. 2003, demonstrating the EC3 0.4 % for MIT is according to the SCCS Opinion the only one published and properly described LLNA assay with MIT. Therefore we consider that there is no need to include references Roberts DW, Patlewicz G, Kern PS,et al. 2007, Estrada E, Patlewicz G, Chamberlain M et al. 2003 and Roberts DW 2013 into CLH report.
- The reference Lundov MD, Zachariae C and Johansen JD. 2011 is already included in the CLH report (See section 4.6.1.2, Table 12).

However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response

The additional information and clarification provided by the Dossier Submitter are noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Sweden	Swedish Contact Dermatitis Research Group	Scientific body	30

Comment received

We agree with the suggested classification of MIT as skin sens. 1A (H317). However, we do not agree with the SCL ≥ 0.06% (600 ppm). The level is, in light of published reports in the scientific literature, much too high.

No rational has been given in the report for the proposed SCL.

We suggest a SCL ≥ 0.0015 (15 ppm, the same as for CMIT/MIT) to protect the workers and consumers in Europe from being sensitised. This proposal is based on the current MIT epidemic in Europe and the knowledge collected from several international scientific publications.

We suggest that products containing MIT, and all other classified skin sensitisers, shall be labelled with the name of the sensitising substance, but with no lower concentration limit. The current CLP requirement to label MIT according to EUH208 down to 1/10 of the GCL or

SCL is not protective enough to prevent elicitation of allergic contact dermatitis in those already sensitised.

Section 4.6.1.1 last paragraph: MIT is a strong sensitiser according to the LLNA, which should be clearly expressed here.

Section 4.6.1.3: Regarding human sensitisation testing (HRIPT, induction) of MIT it is stated in the report that "Given the lack of dose-response in this study, it's suitability for defining an SCL is questionable". This statement is correct, HRIPT for MIT is not to be used for classification.

Section 4.6.1.3 4th paragraph: The report states that "It has to be stressed that cosmetic products are intentionally applied to the skin and at higher doses, that is why setting the lower maximum concentration seems reasonable for cosmetic products." We disagree with this statement! Several occupational groups are exposed multiple times per day to multiple products and mixtures containing MIT, such as detergents, metal working fluids, paints, industrial hand cleansers, and dishwashing liquids, as well as liquid hand soap. These workers cannot avoid this exposure, since it is part of their work. The use concentrations of MIT in mixtures under CLP may be both lower and higher than in cosmetic products (current concentration limit in cosmetics is 0.01%, 100 ppm).

It was recently shown that exposure to liquid hand soap (50 or 100 ppm) during 20 seconds five times per day, as by hand washing, elicited allergic contact dermatitis in 90% of MIT-allergic individuals (Yazar et al 2015). No safe limit has been proven.

Section 4.6.1.5 Conclusions on classification and labelling: "In addition, based on skin sensitisation studies in animals and humans setting lower specific concentrations limits for skin sensitisation of 0.06% seems justified." We agree that a SCL is needed, but we disagree with this statement. 0.06% (600 ppm) has not been justified. In the CLH report the authors have also clearly stated that the human induction study (HRIPT and possibly other) is not suitable for defining an SCL. Furthermore, data from scientific literature regarding exposure levels of MIT in products that have sensitised and elicited allergic contact dermatitis in patients, is in the range of 0.001-0.0021% (10-21 ppm) (Vauhkala et al 2015). This shows that the SCL must be set at a much lower level!

Individuals who are sensitised need to avoid further skin exposure to the allergen. Large proportions of sensitised individuals react at skin exposure to very low concentrations (elicitation threshold). The current EUH208 is not protective enough if the SCL is set according to the proposal. We suggest that MIT shall be labelled according to EUH208, but with no lower limit. This is already required for isocyanates and epoxy (mw ≤700) by EUH204 and EUH205. The name of preservatives need to be labelled according to the Detergents Regulation, and all ingredients (except fragrances) are labelled according to the Cosmetics Regulation.

This response was written by Assoc. Professor Anneli Julander and Professor Carola Lidén on behalf of the Swedish Contact Dermatitis Research Group, and it was agreed on by all its members.

References:
A.K. Vauhkala et al 2015 "Occupational contact allergy to metylchloroisothiazolinone/metylizothiazolinone and metylizothiazolinone" Contact Dermatitis vol 73:150-156

K. Yazar et al 2015 "Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study" British Journal of Dermatology, vol 173:115-122

J.F. Schwensen et al 2014 "Metylisothiazolinone and benzisothiazolinone are widely used in in paint: a multicentre study of paints from five European countries" Contact Dermatitis vol 72:127-138

U.F. Friis et al 2014 "Isothiazolinones in commercial products at Danish workplaces" Contact Dermatitis vol 71:65–74

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

We agree with the proposal that all products containing MIT should be labelled with EUH208: "Contains 2-methylisothiazol-3(2H)-one. May produce an allergic reaction."
Section 4.6.1.: in last paragraph it is mentioned that MIT is a strong sensitiser in the phrase: In a Guinea pig skin sensitisation test MIT was reported to be a weak sensitiser (Bruze et al, 1987), but a strong one (EC = 0.4 % MIT in acetone:olive oil) in mouse local lymph node assay (Basketter et al., 2003).
Section 4.6.1.3: your opinion on occupational exposure versus exposure through cosmetic use is agreed.

RAC's response

The information supporting a much lower SCL for skin sensitisation classification and no limit for the additional label are noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	31

Comment received

CLH-Report, Chapter 4.6 p. 37 f
Considering all available data suitable for classification, we do agree to classify MIT as skin sensitiser subcategory 1A.

Referring to potency and the setting of specific concentration limits, the CLP Guidance, section 3.4.2.2.5s:
"SCLs for skin sensitisation can be set based on the results from animal testing. SCLs are set on the basis of testing of the substance and never on the basis of testing of a mixture containing the sensitising substance (see CLP Annex I, 3.4.3.1.1). Setting of SCL is based on potency; potency is already considered for subcategorisation defining generic concentration limits. SCL generally applies for the most potent skin sensitisers classified in 1A."

By directly comparing the CLP criteria for potency with the data presented for MIT the appropriate potency classification for MIT is „strong" based on conduct of 2 LLNA studies with reported EC3 values of 0.4 and 0.76% and further supported by the Buehler and Magnusson-Kligman assays.

Based on this potency classification the GCL of 0.1% would apply according to Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.0 November 2013, p.365 (Table 3.4.2-i).
In addition to the use of animal data for setting the SCL, the guidance says: "SCLs shall be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL for classification.... Reliable data could be human data from e.g. work place studies where the exposure is defined."
Prevalence data and clinical data point to the sub-categorisation as 1A, however, the data cannot be considered as reliable, and therefore suitable for setting an SCL, as evidenced by the guidance, since the exposure at which induction occurred has not been defined. The only defined human data that could be used for setting the specific concentration limits i.e. where exposure has been controlled, would be the human repeat insult patch test (HRIPT) data provided. In addition, use of ROAT data in already sensitised patients is not suitable as this is describing elicitation and not induction. Such an approach has previously been adopted by RAC for a substance with a similar dataset to MIT, there would therefore be a precedence for this rationale.

From a scientific standpoint the robustness of much of the human data presented and it's suitability for classification purposes should be questioned, as many of the reports were not peer reviewed, adequate reporting and presentation of data is lacking, and exposure was not sufficiently characterized.
In summary, the animal data suggest the potency categorization of ‚strong' is applicable to MIT and the GCL of 0.1% should be applied given the lack of suitable data to suggest otherwise. In addition, the elicitation labelling limit following the 2nd ATP to be applied from June 2015 would be 0.01% and would warn potentially sensitised persons of the presence of MIT in a product above this level.

Page 42 f.
Extensive reference is made to the cosmetic use of MIT and single case-reports are cited from the cosmetic area. It should be noted that the use in cosmetics is ruled under a different regulation and cosmetic products are not subject of CLP.
CLP, preliminary remark no.11. "This Regulation should, as a general principle, apply to all substances and mixtures supplied in the Community, except where other Community legislation lays down more specific rules on classification and labelling, such as Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (1), [...]"

Dossier Submitter's Response

Thank you for supporting the classification of MIT Skin sens. 1A.

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

Our opinion is that due to the wide use of MIT, not only data of biocidal MIT uses, but also data on MIT induced skin sensitisation, resulting from exposure to cosmetics, should be included in the CLH report. Besides that the SCCS opinions on MIT, which were prepared relating to the human safety in relation to MIT exposure through cosmetics, very extensively summarized all the available information that is also relevant regarding the CLH report. Therefore we consider that in this case the inclusion of data regarding health effects

assumed to be induced by MIT containing cosmetic products is justified.
RAC's response
The comments are noted, but in consideration of the basis used previously for setting a SCL for the related substance (CMIT) and the overwhelming weight of evidence pointing to similar very high potency of MIT, an SCL based on human evidence does seem justified.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Sweden	Institute of Environmental Medicine, Karolinska Institutet	Academic institution	32

Comment received

Summary

• The use of Methylisothiazolinone (MIT) in concentrations of 100 ppm and below in cosmetics and in approximately 100 ppm in chemical mixtures such as wall paints has led to a dramatic increase of contact allergy to MIT in Europe.

• Therefore, the current proposal of an SCL of 600 ppm (0.06%) for skin sensitisation shoots high above the target and WILL NOT be sufficient to protect European citizens.

• Due to lack of knowledge regarding a safe concentration, we propose that the SCL for sensitisation shall be 15 ppm, the same as for (CMIT/MIT).

Comments on "4.6.1.3 Summary and discussion of skin sensitisation"

The predictive sensitisation studies (human and animal) referred to in this document have failed to assess the true hazard and potency of MIT as skin sensitiser. Thus, it is certainly not suitable to define a SCL based on these studies.

In recent years, a wealth of clinical studies from different parts of Europe have shown that allergy to MIT has increased dramatically (reviewed by e.g. SCCS 2013 and 2015). This increase is probably the most dramatic in modern time compared to other important allergens. Important sources are cosmetics and chemical mixtures such as paints. MIT has been allowed and used in up to 100 ppm in cosmetics, and wall paints on the European market typically contain 25-150 ppm (Schwensen 2015). In addition, a recent rinse-off use test found that nearly all MIT-allergic subjects (90%) developed allergic contact dermatitis from a liquid hand soap containing 100 or 50 ppm MIT, by exposure for 20 seconds five times per day (Yazar 2015). Thus, there is strong evidence from both clinical and experimental studies that the current use concentrations are not safe, neither for induction nor elicitation, and that the SCL for skin sensitisation should be far below 100 ppm.

The dossier argues that the SCL could be higher than the maximum allowed concentration in cosmetics because cosmetics are "intentionally applied to the skin and at higher doses". We do not agree. Several occupational groups have frequent skin contact with allergens in the products (mixtures) they use, for example paints, detergents and metal working fluids, which are accumulated on the skin during the workday. Unlike the voluntary use of cosmetics, these workers don't have a choice; they are required to use these products in order fulfil their work task. Being sensitised or suffering from allergic contact dermatitis does often result in far-reaching, negative consequences for the worker such as impaired quality of life, recurrent sick leave, and even change of occupation. In other words, this

generates large costs both for society and the individual. Thus, clinically relevant and protective package labelling and information in safety data sheets is crucial in order to avoid harmful exposures.

The current CLP requirement to label according to EUH208 down to 1/10 of a GCL or SCL is not protective enough. Large proportions of sensitised individuals react at skin exposure to very low concentrations (elicitation threshold). They need to avoid skin exposure to avoid dermatitis (elicitation). We suggest that MIT shall be labelled according to EUH208, but without any lower concentration limit. This is already required for isocyanates (EUH204) and epoxy (EUH205). Other examples with no lower concentration limits are the Detergents Regulation where the name of preservatives always needs to be labelled, and the Cosmetics Regulation where all ingredients (except some fragrances) must be labelled. We are convinced that it would be beneficial for prevention of allergy and dermatitis in European consumers and workers if this principle was applied also for MIT, as well as for other classified skin sensitisers.

This response was written by Kerem Yazar, PhD, Assoc. Professor Anneli Julander, and Professor Carola Lidén on behalf of the Institute of Environmental Medicine, Karolinska Institutet, Sweden.

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Yazar K, Lundov M D, Faurschou A, Matura M, Boman A, Johansen J D, Liden C. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study. Br J Dermatol 2015: 173: 115-122.

ECHA note: the following confidential attachment was provided with the comment above:

- *Yazar K., Lundov M.D., Faurschou A.,Matura M., Boman A., Johansen J.D. and Liden C., Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study.*

Dossier Submitter's Response

See response to comment 1.
Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.
We also support your proposal that all product containing MIT, alone or in mixture, should be labelled according to EUH208 without the lower concentration limit.

RAC's response
The additional information is noted. RAC agrees with the perspective expressed in this comment.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Sweden		MemberState	33

Comment received

The CLH proposal
In the CLH proposal for MI classification as Skin Sens 1A is proposed. This is very adequate, based on both animal and human data.
The proposal also include an SCL of 600 ppm; even though the basis for the proposed value is not clear. 600 ppm is not protective, neither for induction nor for elicitation of contact allergy. Below is the reasoning for a lower SCL.
There has been efforts to derive safe concentrations from animal data and HRIPT studies. This has not been successful due to e.g. lack of validation of methods for the purpose and no consensus on choice of safety factors. In the actual case of MI the HRIPT assays have e.g. not been conducted with maximised challenge concentrations, making the results unreliable. In practice the following data on diagnostic patch test frequencies and exposure demonstrate that 600 ppm is not a protective SCL.
During recent years diagnostic patch testing with MI in different European clinics has shown a dramatic increase in sensitisation frequency. The latest reported frequencies are up to around 6% positive patch tests in consecutive dermatitis patients (e.g. Geier et al. 2012, Urwin et al. 2013, Goncalo et al. 2013, Lundov et al. 2013), in some clinics even higher rates (e.g. Aerts et al. 2014, Liuti et al. 2014). Sensitisation may have occurred through occupational exposure or consumer exposure to products like paints, household products or cosmetics.
MI is listed in Annex V of the Cosmetics Regulation with a limitation of maximum 100 ppm as a preservative in cosmetics. The limitation was introduced in the former Cosmetics Directive in 2005. In a publication by Schwensen et al. 2015 concentration of MI in paints was found to vary between 0.7-181 ppm in five European countries.
Taken together it is clear that levels far below 600 ppm have caused the recent dramatic increase of contact allergy in consumers and professionals. Thus the proposed SCL of 600 ppm is too high and will not be protective for sensitisation or elicitation.

Alternative SCL proposal
According to the SCCS Opinion 2015 clinical data and/or elicitation low effect levels are the only methods that have proven efficient in reducing or preventing existing problems of sensitisation in the consumer. Such testing for elicitation low effect levels was conducted by Yazar et al. 2015. A Repeated Open Application Test, ROAT, was conducted with a rinse off-like exposure on MI allergic patients; liquid soap with 100 or 50 ppm was applied for 20 seconds, 5 times per day until a positive reaction was seen or up to 21 days. 10/10 and 7/9, respectively, had positive reactions. Remarkably all patients reacted to 100 ppm and 7/9 patients to 50 ppm at short rinse off-exposures. Thus the ED10, which is a commonly used value to identify an elicitation threshold (the eliciting dose where 10% of tested allergics react to the sensitiser) could be expected to be well below 50 ppm.
Work place and consumer exposure to MI in paints is a well known source to MI sensitisation. Contamination of clothes and parts of the body with paints during a work day will mimic a leave on exposure. It gives further emphasis to an ED10 well below 50 ppm and the necessity to keep the MI concentration as low as possible.
Further support is given by Lundov et al. 2011. A ROAT was conducted with a leave on-like exposure on MI sensitised individuals; a cream preserved with 100 ppm, 50 ppm or 5 ppm MI was applied twice a day for up to 21 days. 7/11, 7/11 and 2/11, respectively, reacted to

the cream. Thus the ED10 was below 5 ppm.
Concentrations of allergens that don't give elicitation reactions among sensitised individuals will normally be safe for induction. However there is no established general relationship between induction and elicitation thresholds. Therefore with the available studies it cannot be excluded that induction may take place down to levels well below 50 ppm. In order to set a safe and protective classification limit we propose an SCL of 15 ppm for MI. This is in consistency with
- the SCL of 15 ppm for MCI/MI, containing 25% MI,
- the SCCS Opinion of 2013 and 2015 where 15 ppm is considered safe for induction in rinse off cosmetic products. For leave on cosmetic products there is no safe level for induction or elicitation,
- the Commission proposal to ban the use of MI in leave on cosmetic products (entry 57 of Annex V to Regulation (EC) No 1223/2009), and the intention of the Commission to propose a further limitation in the Cosmetics Regulation by end of September, i.e. limiting the use of MI in rinse off cosmetic products to 15 ppm,
http://ec.europa.eu/DocsRoom/documents/11677.

Proposal for specific labelling
Due to the sometimes extremely low elicitation thresholds and in order to improve product information on chemical products for those who are sensitised a declaration of any sensitiser present in the product would be useful. It would make it possible for sensitised individuals to avoid elicitation reactions and maintenance of dermatitis. Current provisions in the CLP are not always sufficient, even when a lower SCL is applied. Therefore we propose that the addition of MI in chemical products should be declared on the label irrespective of its concentration. This is in analogy with the special provisions for labelling of isocyanates and epoxy constituents in 2.4 and 2.5 of Annex II of the CLP. The following is proposed to be inserted:
2.X. Mixtures containing methylisothiazolinone
Unless already identified on the label of the packaging, mixtures containing methylisothiazolinone shall bear the following statement:
EUHXXX — 'Contains methylisothiazolinone. May produce an allergic reaction.'

Additionally
Please include the publications by Yazar et al. 2015 and Schwensen et al. 2015 in the CLH proposal.

In summary
• Classification of MI as Skin Sens. 1A is adequate.
• Proposals:
- set an SCL of 15 ppm,
- add special provisions for labelling in Annex II of CLP and
- include the publications by Yazar et al. 2015 and Schwensen et al. 2015 in the CLH proposal.

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• Geier J, Lessmann H, Schnuch A, Uter W. (2012) Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? Contact Dermatitis 67: 334-41
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• SCCS Opinion SCCS/1521/13 (12 December 2013 with revision 27 March 2014)
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• Urwin, R. & Wilkinson, M. (2013) Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new "epidemic". Contact dermatitis 68: 253–5
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Dossier Submitter's Response

See response to comment 1..

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

We agree with the labelling of MIT containing products with EUH208 without a lower concentration limit.

RAC's response

The additional information is noted. RAC agrees with the perspective expressed in this comment.

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2015	Switzerland	Dow Europe GmbH	Company-Manufacturer	34

Comment received

We agree with the proposed subcategorization of MIT as Cat. 1A however we propose the GCL of 0.1% for strong sensitisers be maintained. On the basis of CLP Regulation and associated guidance, the animal data suggest the potency categorization of ‚strong' is applicable to MIT and the GCL of 0.1% should be applied given the lack of data suitable for classification purposes, to propose otherwise. See attachment.

ECHA note: The following attachment was provided with the comment above:
- *Dow comments to MIT CLH proposal*

Dossier Submitter's Response

Considering the rising number of studies reporting increasing incidence of confirmed MIT sensitised individuals, skin sensitising reactions to MIT at doses below 600 ppm and wide use of MIT in industrial and consumer products the weight evidence shows that 0.1 % and even 0.06 % concentration of MIT is not the satisfactory specific concentration limit for classification of MIT as Skin Sens. 1A, H317, to protect sensitised individuals from

elicitation of skin sensitisation.

Even though MIT is considered to be a strong skin sensitiser, according to results of skin sensitisation studies performed in experimental animals and criteria on assessing the potency of substance being tested in the Guidance on the Application of the CLP criteria, we consider that the recommended generic concentration limit 0.1 % is not protecteive enough as already described in the text above.

In document Industry submission to CLH public consultation on 2-methyl-2H-isothiazol-3-one criteria for sub-categorisation 1A for skin sensitisation in Table 1, Guinea pig maximisation test are not complete. Positive response in more than 60 % of animals intradermaly induced with ≤ 0.1 % test substance is also triggering the classification skin sensitiser 1A.
In Thor Guinea pig maximisation test 100 % animals responded positively to 0.1 % MIT intradermal induction dose and not to 1 % MIT as erroneously presented in Table 2 of document with comments to CLH proposal.

RAC's response

RAC notes the comment and additional information but, like the Dossier Submitter, considers other data supporting a specific concentration limit to be overwhelming.

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2015	Norway		MemberState	35

Comment received

We support the classification of MI(T) with Skin Sens 1A; H317 based on the skin sensitisation studies in animals and human data. Furthermore, we agree on the need of setting a lower specific concentration limit (SCL) for this effect. However, we question whether the proposed SCL (600 ppm) is conservative enough.

We are concerned about the rapid increase in incidences of MIT induced allergies observed in several countries due to widespread use of consumer products containing MIT. The concentration of MIT in most MIT containing products on the marked seems to be equal to or below 100 ppm (ref: the Risk Management Option report on MIT of 13 March 2015 (Danish EPA). The Scientific Committee for Consumer Safety (SCCS) concluded in their opinion of March 2014 that: "The wealth of clinical data demonstrates that 100 ppm MI sensitises." (SCCS/1521/13). Thus, is seems reasonable to set a SCL for the classification of MIT as a skin sensitiser (H317) below 100 ppm (resulting in special label provision for already sensitised individuals of 1/10 of this limit). This will give a better protection to already sensitised persons and will help consumers take individual precautions in handling of MIT containing consumer products.

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response

RAC agrees that a lower specific concentration limit than 100ppm is justified for

classification. An even lower labelling limit to protect already sensitised individuals is also appropriate.

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2015	Germany		MemberState	36

Comment received

Based on studies in animals and humans the dossier submitter proposes setting a specific concentration limit (SCL) of 0.06 % (corresponding to 600 ppm) for skin sensitisation, admitting that this SCL may not be protective enough for some pre-sensitised individuals.

The proposal of setting a SCL of 0.06 % (or 600 ppm) for skin sensitisation of MIT is not supported due to several reasons:

(1) It is not understandable why the dossier submitter proposes a SCL of 0.06 % in the awareness that this concentration does not protect from skin sensitisation. This makes the introduction of a SCL useless.

(2) The derivation of the SCL is not well substantiated. Apparently, the value of 0.06 % was derived from human studies described on p. 42, where MIT was a skin sensitiser when used in concentrations up to 0.05 % (500 ppm), but not at 0.06 %, but at the same time the dossier submitter questions these data from human studies ("The study is designed to maximise exposure to the test substance to try to generate a response, the exposure is repeated nine times over a 21 days period and involves occlusion and can be considered an extreme exposure scenario. In addition, the study uses a formulated product diluted in water which may affect the sensitisation potential due to vehicle effects. Given the lack of dose-response in this study, its suitability for defining an SCL is questionable".)
Therefore the dossier submitter is asked to clarify which data the SCL of 0.06 % is based on.

(3) The dossier submitter questions data demonstrating that concentrations below 0.06 % cause skin sensitisation. In view of the dramatic rise of contact allergy to MIT based on the allowed use concentration of 100 ppm (0.01 %) in cosmetic leave-on and rinse-off products, the Scientific Committee on Consumer Safety (SCCS) concluded in document SCCS/1521/13 (SCCS, 2014) that "current clinical data indicate that 100 ppm MI in cosmetic products is not safe for the consumer. For leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the view of induction of contact allergy." The dossier submitter made a general statement (apparently on the studies used in SCCS/1521/13) that "from a scientific point of view the robustness of these data and their suitability for classification purposes is questioned, as many of the reports were not peer reviewed, adequate reporting and presentation of data is lacking, and exposure was not sufficiently characterized."
A more elaborate justification on the disqualification of the studies should be given by the dossier submitter.

When comparing arguments listed in (2) and (3), the dossier submitter disqualified studies used for setting a specific concentrations limit and also disqualified studies indicating that the proposed SCL of 0.06 % might not be sufficient.

(4) In the meantime, further information has become available.

- In a study published in February 2015, 19 MIT-allergic subjects and 19 controls without MI allergy applied 2 liquid hand soaps five times per day on areas of 5*10 cm on the ventral side of their forearms. One soap contained 100 ppm MIT (0.01 %), the maximum allowed concentration in cosmetics, and was used by 10 allergic subjects and all controls. Another liquid soap with 50 ppm MIT (0.005%) was used by 9 allergic subjects. As the negative control, all subjects used a similar soap that did not contain MIT. The repeated open applications (ROAT) proceeded for up to 21 days or until a positive reaction occurred. The study was conducted in a randomised and blinded fashion. Ten (10) out of 10 MIT-allergic subjects developed positive reactions to the soap with 100 ppm and 7 out of 9 reacted to the 50 ppm soap, while none of the 19 controls had a positive reaction during 21 days of application (p=0.0001). The authors concluded that rinse-off products preserved with 50 ppm MIT or more are not safe for consumers. A no-effect level was not determined (Yazar et al., 2015; SCCS, 2015; Goncalo, M. (2015)).

- A recent report from UK indicates that MIT sensitisation might still be possible even after a possible ban of MIT from leave-on cosmetic products and limiting the concentration to 15 ppm (0.0015 %) in rinse-off cosmetic products (Warburton an Wilkinson, 2015).

In addition to cosmetics, the consumer is exposed to various sources of MIT/CMIT. These active substances are used as biocides in industrial products such as dispersion paints and lacquer, for protection of baits and in household cleaning products. In a recent review it is stated for MIT that the current increase in sensitisation rates over the last three years has been dramatic (Mahler et al., 2014). The prevalence of sensitisation to MIT ranges from 0.5% to 6% depending on the study and the trend is rising (Leiva-Salinas et al., 2014). According to the current "hit list" of contact allergens in the patch test (age- and gender-standardized, database status: 8th November 2013, DKG-IVDK consortium), CMIT/MIT is at position 6 of all contact allergens. It is further suspected that the high incidence could rely on immunologic cross reaction of MIT to CMIT. This is reflected by the fact that in human patch test two-thirds of MIT positive patients are CMIT/MIT positive. Although it is not known for sure what the primary sensitiser is, MIT alone can undoubtedly induce and elicit contact allergic reaction (Lundov et al., 2011). With regard to animal studies, MIT was previously classified by local lymph node test as a moderate sensitiser. In contrast, it was subsequently shown that the results pointed to MI not as a moderate but as a strong sensitiser (Leiva-Salinas et al., 2014). Studies using guinea pig and mice further revealed a sensitising potency below 40 ppm (corr. active ingridient after re-challenge). This concentration is by a factor of 15 far away from the SCL of 0.06 (600 ppm) proposed by dossier submitter.

A broad and altered exposure can be assumed for the consumer and protection against induction of allergic contact dermatitis is only one part of the problem. In a scenario where the incidence of MIT associated contact allergy increases in the general population, elicitation of an existing, abundant species of allergy has to be prevented as well. High incidence was also reported in studies on patients with eczema and underlines the marked allergenicity of these substances.

The German CA supports the approach to derive an Acceptable Exposure Concentration (AEC) for CMIT/MIT based on the No Expected Sensitisation Induction Level (NESIL) of 10 ppm according Human Repeat Insult Patch tests data on CMIT/MIT and MIT (SCCS Opinion, 27 March 2014).

In summary, for MIT the SCL should be set to 0.001 %.

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Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response

RAC agrees that 600ppm would not be a protective limit and that the available human data should be assessed to identify a more appropriate level.

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2015	Germany	University of Onsabrück/StanDerm Action	Academic institution	37

Comment received

Statement of EU Horizon 2020 COST Action TD 1206
"Development and Implementation of European Standards on Prevention of

Occupational Skin Diseases (StanDerm)"

The following statement is being issued by the COST Action TD 1206 "Development and implementation of European Standards on prevention of occupational skin diseases" (StanDerm), which comprises over 140 experts from dermatology, allergology, epidemiology, occupational medicine and health education of 28 European countries and Turkey. It bundles inter-disciplinary research relevant for prevention of occupational skin diseases (OSD) in the participating countries, including basic sciences, epidemiological surveillance, translational and applied clinical research. Primary prevention of allergy elicitation is an essential task of safety and health at work.

In Europe, occupational skin diseases (OSD) represent meanwhile up to 35% of all occupational diseases. OSD related costs exceed 5 billion €/year in the EU by loss of productivity and cause extensive suffering for affected workers and may even lead to job-loss due to acquired occupational allergies and late intervention. This concerns particularly small and medium-sized enterprises as they often have limited technical expertise and lack dedicated OSH specialists.

There is growing concern because of an epidemic increase of incidence rates of MIT allergy over the past years. This relates particularly to the exposure to products at the workplace containing MCIT/MIT. A high proportion of sensitised workers are in jeopardy of job loss; this fact is particularly relevant as contact allergy against MCIT/MIT may be elicited also by airborne exposure at workplaces.

Having therefore considered the CLH report for 2-methylisothiazol-3(2H)-one (MIT), we agree with the classification of MIT as skin sens. 1A, H317 and that the specific concentration limit should be lower than 0.1%. However, based on our extensive clinical experience, we believe that the proposed threshold concentration of 0.06% is definitely not low enough to protect workers and consumers from skin sensitisation. Workplace exposure to products potentially containing MIT is continuous and very often unavoidable and therefore judicious use concentrations and adequate risk phrasing and labeling requirements are crucial.

With regard to the special labelling requirements for mixtures not being classified for skin sensitisation but containing MIT, we draw attention to the fact that the proposed concentration limit for the labelling 0.006% is not low enough to protect sensitised workers and consumers from elicitation of allergic contact dermatitis. The concentration limit for MIT requiring to be mentioned on the package (and in safety data sheets), i.e., for labelling, should be at least the same as that of MCIT/MIT.

Maximum benefit in terms of secondary prevention of MIT sensitised persons would be achieved if the presence of MIT is declared with the name of the substance according to EUH208, but with no lower concentration limit. The current CLP requirement to label according to EUH208 down to 1/10 of the GCL or SCL is not protective enough. Labelling at all concentrations is required for isocyanates and epoxy by EUH204 and EUH205. The name of preservatives needs to be labelled according to the Detergents Regulation, and all ingredients (except fragrances) are labelled according to the Cosmetics Regulation.

We furthermore note that the proposed concentration limits for classification and labelling do not take into account recent research findings, and that threshold concentration levels should be updated according to these.

The literature below pinpoints that there has been up to a six-fold increase of occupational

allergies, including contact dermatitis, being generated by MIT and MCIT/MIT- Liquid soaps, industrial hand cleansers, detergents, skin care products, paints, metal-working fluids and their biocides, as well as fountain solution additives in printing work are the most common sources of exposure to MIT or MCIT/MIT. Often, products containing MIT or MCIT/MIT are not labelled or mentioned in the safety data sheets or product declarations.

These research findings are supported by data obtained in the IVDK network (www.ivdk.org), which is a Swiss/German/Austrian consortium: Between 2009 and 2012 the prevalence of MIT sensitisation, when tested in a preservatives test series (in about 60% of all patients) tripled from about 2% to 6%. In 2014, the prevalence in 12,297 consecutive (all) patients was found to be 6.3% (pers. comm. J. Geier). IVDK tests MIT at a 0.05% concentration, which is at the lowest end of the presently used range of test concentrations (0.05 to 0.2%) and may thus under-diagnose sensitisation to some extent.

It is also important to note that once sensitised (by whichever route or product type), even airborne exposure to vapours of drying paint containing MI can lead to severe allergic contact dermatitis of exposed skin (mostly face, hands and arms) as proven by multiple case reports and daily clinical experience.

To summarize, occupational exposures to products containing MIT or MICT/MIT may be much more intense than cosmetic exposures and therefore the limits (for attributing the H317 risk phrase and for labeling MIT, respectively) should definitely not be higher than the presently recommended maximum use concentrations for rinse-off cosmetics (see SCCS/1521/13).

The above statement represents the current scientific knowledge in Europe and is essential to be considered for threshold concentration limits for worker and consumer safety.

For the members of the EU Horizon 2020 Cost Action "Development And Implementation Of European Standards On Prevention Of Occupational Skin Diseases (Standerm)"(TD1206) (http://www.cost.eu/COST_Actions/isch/Actions/TD1206?management)

Swen Malte JOHN, chair
Sanja KEZIC, vice-chair

Literature:

Ackermann L, Aalto-Korte K, Alanko K, Hasan T et al. Contact sensitisation to methylisothiazolinone in Finland – a multicentre study. Contact Dermatitis 2010: 64: 49-53.

Alwan W, White IR, Banerjee P. Presumed airborne contact allergy to methylisothiazolinone causing acute severe facial dermatitis and respiratory difficulty. Contact Dermatitis. 2014 May;70(5):320-1

Lammintausta K, Aalto-Korte K, Ackermann L, Alanko K et al. An epidemic of contact allergy to methylisothiazolinone in Finland. Contact Dermatitis 2014: 70: 184-185.

Lundov M D, Thyssen J P, Zachariae C, Johansen J D. Prevalence and cause of methylisothiazolinone contact allergy. Contact Dermatitis 2010: 63: 164-167

Lundov MD, Zachariae C, Johansen JD. Methylisothiazolinone contact allergy and dose-response relationships. Contact Dermatitis. 2011 Jun;64(6):330-6.

Lundov MD, Mosbech H, Thyssen JP, Menné T, Zachariae C. Two cases of airborne allergic contact dermatitis caused by methylisothiazolinone in paint. Contact Dermatitis. 2011 Sep;65(3):176-9

Lundov MD, Friis UF, Menné T, Johansen JD. Methylisothiazolinone in paint forces a patient out of her apartment. Contact Dermatitis. 2013 Oct;69(4):252-3

Lundov MD, Kolarik B, Bossi R, Gunnarsen L, Johansen JD. Emission of isothiazolinones from water-based paints. Environ Sci Technol. 2014 Jun 17;48(12):6989-94

Mose A P, Lundov M D, Zachariae C et al. Occupational contact dermatitis in painters – an analysis of patch test data from the Danish Contact Dermatitis Group. Contact Dermatitis 2012: 67: 293-297.

Schwensen J F, Menné T, Veien N K, Funding A T et al. Occupational contact dermatitis in blue-collar workers: results from a multicentre study from the Danish Contact Dermatitis Group (2003-2012). Contact Dermatitis 2014: 71: 348-355.

Schwensen J F, Lundov M D, Bossi R, Banerjee P et al. Methylisothiazolinone and benzisothiazolinone are widely used in paint: a multicentre study of paints from five European countries. Contact Dermatitis 2014:72:127-138.

Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitisation. Contact Dermatitis 2013: 69: 231-238.;

Vauhkala AR, Pesonen M, Suomela S, Kuuliala O, Suuronen K, Aalto-Korte K. Occupational contact allergy to methylchloroisothiazolinone/ methylisothiazolinone and methylisothiazolinone. Contact Dermatitis. 2015 73:150-6.

Yazar K, Lundov MD, Faurschou A, Matura M, Boman A, Johansen JD, Lidén C. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-appl ication study. Br J Dermatol. 2015 Jul;173(1):115-22.

ECHA note: An attachment was submitted with the comment above. As it contains the same content as the comment, it is not provided as a separate attachment.

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

We also support the classification of all MIT containing products, alone or in mixture, to be classified according to the EUH208 without lower concentration for classification or with a specific EUH phrases as is the case for isocyanates and epoxy constituents.

RAC's response

Noted. RAC agrees that the available human data and the SCCS recommendation support a much lower limit than originally proposed by the Dossier Submitter.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-METHYLISOTHIAZOL-3(2H)-ONE (ISO)

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	38
Comment received				
A classification for skin sensitisation in Category 1A is proposed with a specific concentration limit of 0.06%. We agree with the classification, but have some comments on the proposed concentration limit. As mentioned in the CLH report, the SCCS concluded in 2013 that a concentration of MIT of 0.01% in leave-on cosmetic products can lead to the induction of contact allergy and is not safe for consumers. This conclusion was not taken over, with the argumentation that cosmetic products are intentionally applied to the skin and at higher doses than other products. We doubt that this is true, because in general occupational exposures are not lower than other uses and may be more frequent leading to aggregated exposure. In addition, as classification is hazard based, conclusions are usually drawn on studies that use intentional exposure at higher doses. The fact that the studies in this case are epidemiological rather than toxicological, does not mean they cannot be used to draw general conclusions as long as they are well performed and documented. Hence, the relatively high exposure from cosmetics does not render the SCCS conclusion that 0.01% is not safe irrelevant. More importantly, no argumentation was provided why 0.06% would be a safe limit for other uses. The concentration of 0.06% seems to be based on only one HRIPT study with human volunteers, of which the authors themselves state that the suitability for defining an SCL was deemed questionable (p42). It is therefore strange that the SCL is based on this study. The data provided on this study (Table 11b) shows that at lower levels, e.g. 0.01, 0.04 and 0.05%, induction occurred. Therefore, we do not understand why the limit was set at 0.06%. In another human volunteer study, no reaction was seen up to 0.05%, but the highest dose group (0.1%) consisted of only 16 subjects, which is insufficient in these type of studies. The size of the other dose groups was not given, making it impossible to draw conclusions on this study. The SCL seems solely based on HRIPT studies that are performed for the producers and of which we do not have the experimental details. We recommend to consider the numerous clinical studies available in open literature as well, which are in detail described in the SCCS opinions of MIT (2014, 2015). These studies provide evidence that 0.01% MIT can induce contact allergy. A large body of clinical evidence showing 0.01% MIT has led to a strong increase in MIT induced contact allergy in recent years has been provided in the latest SCCS opinions (Submission II, 2014 and Submission III, 2015). In addition to the studies already included in the CLH report, the opinion mentions the following recent studies: - Hosteing S, Meyer N, Waton J, Barbaud A, Bourrain JL, Raison-Peyron N et al. Outbreak of contact sensitisation to methylisothiazolinone:an analysis of French data from the REVIDAL-GERDA network. Contact Dermatitis 2014; 70: 262-269 - Aerts O, Baeck M, Constandt L, Dezfoulian B, Jacobs MC, Kerre S, Lapeere H, Pierret L, Wouters K, Goossens A. The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicenter study. Contact Dermatitis 2014; 71: 41-48 - Madsen JT, Andersen KE. Further evidence of the methylisothiazolinone epidemic. Contact Dermatitis. 2014; 70: 246-247 - Johnston GA, contributing members of the British Society for Cutaneous A. The rise in				

prevalence of contact allergy to methylisothiazolinone in the British Isles. Contact Dermatitis 2014:70(4):238-40
- de Wit-Bos L, Kooi MW, Bourgeois FC, van Gorcum TF. Cosmetovigilance in The Netherlands Overview of the period 2009-2014. RIVM report 2014-0025

These studies show a strong increase in the incidence of MIT induced allergic contact dermatitis in recent years. Diagnostics patch tests by themselves do not prove which products caused the induction or at which dose levels. However, the location of the dermatitis (face and hands), exposure information provided by the patients, and the relatively large percentage of woman involved, indicate that cosmetics were the allergen source in a majority of the cases. As the currently allowed concentration MIT in cosmetics is 0.01%, it can be concluded that this concentration sensitises. The SCCS concluded that on the current information it is not possible to derive a safe concentration MIT in leave-on products, while the safe concentration limit of 0.0015% for rinse-off products is based on CMIT/MIT.

It should also be considered that, while cosmetics are the most important source of MIT induced allergies, there have been also an appreciable number of cases reported caused by paints and cleaning agents. In some of these cases, elicitation of allergic contact dermatitis occurred after airborne exposure, particularly to paints. While these studies were reported under respiratory sensitisation (p45-46), they are actually cases of skin sensitisation as this was the organ where the reaction occurred. An additional study from the opinion of CMIT/MIT showed a surge of dermatitis after occupational exposure to paint which contained MIT as additive (Thyssen et al., 2006).
According to a screening study of paints on the market, the concentration MIT in paint ranges from 0.7-180.9 ppm (0.00007-0.018%) (Schwensen et al., 2015). Thus, there are strong indications that a concentration of ~0.01% not only leads to sensitisation when used in cosmetics, but also in other products.

A concentration limit of 0.06% would also be too high to warn people who are already sensitised to MIT. A recent study on MIT sensitised consumers showed positive reactions of 10/10 subjects on 0.01% and 7/9 subjects on 0.005% MIT in soap. This means that the proposed concentration of 0.006% at which labelling would be required, is not adequate to inform the sensitised population.
(Yazar K, Lundov MD, Faurschou A, Matura M, Boman A, Johansen JD, Liden C. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: A Repeated Open Application study. Br J Dermatol 2015: Accepted)

In conclusion, as it is shown by growing number of studies that a concentration of 0.01% in cosmetics has led to an increase in the incidence of contact allergies, a concentration limit 0.06% is too high. Based on the epidemiologic data showing the increase in skin sensitisation after exposure to concentrations up to 100 ppm (0.01%), an SCL of 0.01% is proposed. A lower SCL may be justifiable if this is supported by new studies.

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response
Noted. RAC agrees that the available human data support a much lower limit than originally proposed by the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Finland	Finnish Institute of Occupational Health	Scientific body	39

Comment received

(1) We agree to the classification of MIT as Skin sens. 1A, H317.

(2) We also agree to that the specific concentration limit should be lower than 0.1%, but our concern is that the proposed specific concentration of 0.06% is not low enough to protect workers and consumers from skin sensitisation.

(3) We also agree to that a special labelling requirement is applied for mixtures not being classified for skin sensitisation, but containing MIT: 'Contains 2-methylisothiazol3(2H)-one. May produce an allergic reaction.' Our concern is that the proposed concentration limit for the labelling 0.006% is not low enough to protect sensitised workers and consumers from elicitation of allergic contact dermatitis.

(4) The proposed concentration limits for classification and labelling are based on old data, and new investigations must be taken into account.

Finland is among the countries affected by the current epidemic of MIT allergy: Lammintausta et al. reported frequency of positive patch test reactions as high as 13.2% for MIT (tested at a concentration of 0.05%) in eight Finnish dermatology clinics during the first five months of 2013 (Lammintausta K, Aalto-Korte K, Ackermann L, Alanko K et al. An epidemic of contact allergy to methylisothiazolinone in Finland. Contact Dermatitis 2014: 70: 184-185.) . In 2006-2008, the corresponding figure was 0.9% for 0.03% MIT and 1.8% for 0.1% MIT (Ackermann L, Aalto-Korte K, Alanko K, Hasan T et al. Contact sensitisation to methylisothiazolinone in Finland – a multicentre study. Contact Dermatitis 2010: 64: 49-53.)

It is difficult to differentiate between MIT allergy and MCIT/MIT allergy, because MIT is constituent of the latter. At the Finnish Institute Occupational Health in a clinical study of MIT and MCIT/MIT allergy, we have observed a six-fold increase in the number of occupational cases in the second half of a study period ranging from January 2002 to February 2013 compared with the first. Liquid soaps, industrial hand cleansers, detergents, skin care products, paints, metal-working fluids and their biocides, and fountain solution additives in printing work were common sources of exposure to MCIT/MIT or MIT. A total of 33% of the patients used MIT or MCIT/MIT-containing products without any mention of MCIT/MIT or MIT in safety data sheets or product declarations. (Vauhkala AR, Pesonen M, Suomela S, Kuuliala O, Suuronen K, Aalto-Korte K. Occupational contact allergy to methylchloroisothiazolinone/ methylisothiazolinone and methylisothiazolinone. Contact Dermatitis. 2015 73:150-6.)

In the Finnish Register of Occupational Diseases, there is a 4−5-fold increase in the number of allergic contact dermatitis cases due to MIT and MCIT/MIT when years 2012 and 2013 are compared with year 2009.

In Finland, the current epidemic of MIT and MCIT/MIT contact allergy exceeds several-fold

any previous epidemic. The independent use of MIT in cosmetics and industrial products is probably the main cause of this epidemic. The process of restricting the use of MIT in cosmetic products has begun,
(http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_145.pdf)
but it is not enough for preventing sensitisation, because consumers and workers are also exposed to other products.

(2) The proposed concentration limit for classification as a skin sensitiser, 0.06%, is not sufficiently low

The literature reports painters and paint factory workers as the most significant occupational group associated with contact allergy to MCIT/MIT or MIT (Lundov M D, Thyssen J P, Zachariae C, Johansen J D. Prevalence and cause of methylisothiazolinone contact allergy. Contact Dermatitis 2010: 63: 164-167.; Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitisation. Contact Dermatitis 2013: 69: 231-238.; Schwensen J F, Menné T, Veien N K, Funding A T et al. Occupational contact dermatitis in blue-collar workers: results from a multicentre study from the Danish Contact Dermatitis Group (2003-2012). Contact Dermatitis 2014: 71: 348-355.) and vice versa, MIT and MCIT/MIT are significant sensitisers among painters (Contact Dermatitis 1995: 32: 39-45.; Mose A P, Lundov M D, Zachariae C et al. Occupational contact dermatitis in painters – an analysis of patch test data from the Danish Contact Dermatitis Group. Contact Dermatitis 2012: 67: 293-297.).
Most water-soluble paints in the European market contain MIT: in a recent European multicenter study 93% of paints contained MIT up to a concentration of 181 p.p.m.(0.018%) (Schwensen J F, Lundov M D, Bossi R, Banerjee P et al. Methylisothiazolinone and benzisothiazolinone are widely used in paint: a multicentre study of paints from five European countries. Contact Dermatitis 2014:72:127-138). This shows that concentrations much below 0.06% in paints sensitise workers using paints. Skin exposure to paints in painting work is similar to leave-on cosmetic products: painters do not constantly remove paint stains from the skin.

Metal-working fluids also often contain MIT or MCIT/MIT. Use of gloves if not allowed at all in metal work in Germany, and in Finland, where the glove use is allowed and recommended, adequate gloves are rarely used at work places. Thus, metal-workers often have prolonged skin contact with the metal-working fluids, which is at least comparable to the use of leave-on cosmetic products or represents even more intense exposure as fluids have repeated contact with skin.

The concentration limit for the classification of MIT should be the same as that of MCIT/MIT, 0.0015% (15 p.p.m.). This limit probably covers the independent use of MIT.

(3) The proposed concentration limit for labelling, 0.06%, is not sufficiently low

At the moment, MIT contact allergy is common in the general population and sensitised individuals have to avoid all skin contact with the chemical.

Recently it has been shown that a concentration of 0.005% (50 p.p.m.) MIT in a liquid soap elicits symptoms in sensitised individuals (Yazar K, Lundov MD, Faurschou A, Matura M, Boman A, Johansen JD, Lidén C. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a
repeated open-application study. Br J Dermatol. 2015 Jul;173(1):115-22.), and the corresponding concentration for a cream was 0.0005% (5p.p.m.) in another study (Lundov

MD, Zachariae C, Johansen JD. Methylisothiazolinone contact allergy and dose-response relationships. Contact Dermatitis. 2011 Jun;64(6):330-6.)

The special concentration limit for labelling should be 0.0015%, if the same limit is not used in classification.

Abstracts of the references (when available) are in an attachment

ECHA note: the following attachment was provided with the comment above:
- *Abstracts of references*

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response

Noted. RAC agrees that the available human data now support a much lower limit than that proposed by the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Denmark		MemberState	40

Comment received

The Danish CA agrees with the proposal to classify for 2- methylisothiazol-3(2H)-one (MIT) for skin sensitisation in category 1A. However, we do not agree with the proposal for setting a specific concentration limit (SCL) of 0.06% (600 ppm) as suggested in the CLH proposal, section 4.6.1.3. The classification proposal presents no specific arguments to support the choice of this particular SCL, but refers to the result of animal and human experimental data, whilst epidemiological data from published articles are considered to lack scientific robustness and are therefore dismissed as unsuitable for classification purposes. The Danish EPA considers that the wealth of available clinical data on sensitisation from MIT makes it clear that the substance causes sensitisation in humans at much lower levels than the SCL of 0.06% proposed by the Slovenian CA. Based on scientific evidence - including the recent opinions from the Scientific Committee for Consumer Safety (SCCS) on MIT from 2014 and 2015 - the Danish CA considers that an SCL of 0.0015% (15ppm) is justified. A more thorough justification for this is provided in the attached document.

ECHA note: The following attachment was provided with the comment above:
- *Danish Comments to the CLH proposal for 2- methylisothiazol-3(2H)-one (MIT), (CAS no 2682-20-4).*

Dossier Submitter's Response

Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined.
However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.

RAC's response
Noted. RAC agrees that the available human data now support a much lower limit than that proposed by the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Finland		MemberState	41
Comment received				
Skin sensitisation: The Finnish CA supports the proposed classification and labelling as Skin Sens. 1A; H317 for 2-methylisothiazol-3(2H)-one. Specific concentration limit for skin sensitisation: In opinion of the Finnish CA the proposed specific concentration limit for 2-methylisothiazol-3(2H)-one has not been adequately discussed and justified. According to the CLH-report both animal and human studies were the basis for the proposed specific concentration limit of 0.06 % for skin sensitisation. However, it has not been discussed how this limit value was chosen or derived. A No-Adverse-Effect Level of 0.06 % (or 30 µg/cm2) has been observed in one of the studies presented in the report, but solely this result cannot be considered as an adequate justification for the proposed specific concentration limit. Questionability of this value has been noted even in the CLH-report.				
Dossier Submitter's Response				
Data and weight of evidence analysis submitted during the public consultation show that our proposed SCL of 0.06% (w/w) for MIT may not be protective enough for sensitised individuals. Therefore the lower SCL shall be defined. However, the Slovenian CA leaves up to the RAC to decide on the most appropriate SCL for MIT.				
RAC's response				
Noted. RAC considers the available human data to justify a lower concentration limit than that proposed by the Dossier Submitter.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2015	Germany	Not applicable	Individual	42
Comment received				
Since 3 1/2 years I suffer from MI and MCI. It is not only containing in cosmetic products like cremes, antitranspirants or hair shampoo, it is an ingredient in wall paintings and fabric conditioner too. I guess it would be helpful to restrict this chemical. There are enough other possibilities to use less harmful preservatives, especially in wall paintings.				
Dossier Submitter's Response				
Thank you for your comments. Unfortunately the purpose of MIT CLH dossier is not restriction of the MIT, but its classification as a skin sensitiser as such and in products containing MIT above a specific concentration limit.				
RAC's response				
Noted. It is anticipated that harmonised classification and labelling of MIT, with a low concentration limit for labelling of mixtures containing MIT, will help to protect people in the future.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	43
Comment received				
No classification is proposed for STOT RE. However, severe effects, including mortality were reported in a 28-day study and a teratogenicity study at relevant concentrations for STOT RE2. As the information provided on the cause of death is very limited, especially for the 28-day study, it is not possible to assess the relevance of these findings. Please provide an explanation why these effects were not sufficient for classification. This could be based on the fact that the LD50 in female rats is in a comparable dose range as the dose levels inducing repeated dose toxicity in the 28-day study and no effects warranting STOT RE were observed in the 90-day studies.				
Dossier Submitter's Response				
According to our opinion the classification of MIT as STOT RE 2 is not justified. In 28-days oral rat study the animals of both sexes treated with high dose of MIT, 71 mg/kg bw/day, were lethargic during week 3 and 4. At this dose 4 animals died, 1 male and 3 females, and decreased body weight and food consumption were observed in males, while no reduction of these paraters was observed in females. Another oral repeated dose study was performed in rats. Animals were exposed to comparable high dose of MIT, 66 mg/kg bw/day, for longer period (90 days), but no mortalities were reported, only slight reduction of body weight, food and water consumption. One of the criteria for classification of a substance as STOT RE 2 is consistent and identifiable toxic effect in humans or experimental animals. Since mortalities observed in 28-days oral rat study were not seen in 90 days oral study, conducted with similar dose of MIT this criteria is not fulfilled. Longer exposure would be expected to result in more severe effects. According to criteria for classification STOT RE 2 clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity are not the bases for classification STOT RE 2. Since only slightly reduced body weight, food and water consumption were observed in 90-days rat study, the classification of MIT as STOT RE 2 is not warranted.				
RAC's response				
RAC notes the additional explanation provided by the Dossier Submitter. Taking into account the LD50 data, as suggested by the comment, it appears that STOT RE 2 is not justified.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	44
Comment received				
CLH-Report, Chapter 4.3 p. 32 f STOT SE 3 or EUH071 Considering all available data, we do agree with the proposed classification with STOT SE 3, H335 (may cause respiratory irritation). In view of the low vapor pressure of the substance and of the intended and reasonably expected conditions of handling and use of the substance, we question the relevance of data obtained by means of artificially maximized aerosol exposure.				

We further do not agree with the discussed classification as corrosive to the respiratory tract (EUH071) based on mechanistically considerations.
Dossier Submitter's Response
In acute inhalation toxicity studies signs of respiratory irritation were observed. Corrosivity of MIT was shown in skin irritation/corrosion studies and corrosivity is clearly the mechanism of pulmonary toxicity in tested animals. Therefore it is justified to propose the classification EUH071, corrosive to the respiratory tract, for MIT. Since EUH071 is assigned to MIT, the classification STOT SE, H335, is redundant.
RAC's response
Since the mechanism of toxicity is likely to be corrosivity, RAC agrees that it would be appropriate to apply the additional labelling phrase EUH071 *("Corrosive to the respiratory tract")*. Although the data suggest that MIT is a respiratory irritant, the effects are accounted for by the classification for acute inhalation toxicity and the application of the EUH071 phrase. Therefore RAC agrees with the DS and considers that additional classification for STOT SE would be redundant.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	45
Comment received				
CLH-Report, Chapter 5.5, p. 91 f. Aquatic Acute 1. M-factor=10 The environmental classification in the CLH-dossier is based on the 24 h values from an algae study. According to the CLP Regulation (Annex I, Part 4, Table 4.1.0) 72 h or 96 h ErC50 values should be used for determining the acute aquatic environmental classification of a substance when taking algae data into account. How can this deviation from the legislation be justified? CLH-Report, Chapter 5.5, p. 91 f. Aquatic Chronic 1, H410. M-factor=1 The environmental classification in the CLH-dossier is based on the 24 h values from an algae study. According to the CLP Regulation (Annex I, Part 4, Table 4.1.0) 72 h or 96 h ErC50 values should be used for determining the chronic aquatic environmental classification of a substance when taking algae data into account. How can this deviation from the legislation be justified? CLH-Report, Chapter 5.5, p. 91 f. Aquatic Chronic 1, H410. M-factor=1 We disagree with the proposed M-factor of 1. It is stated that MIT can be regarded as rapidly biodegradable because its degradation products are rapidly biodegradable and less toxic than the parent compound. Thus, based on the relevant NOErC value from the algae study with S. costatum, no chronic M-factor should be applied.				
Dossier Submitter's Response				
First we would like to emphasize that we have given for chronic classification preference to EC10 endpoints rather than NOEC values. EC10 values are derived from the dose-response curve and as such statistically more robust and less affected by variability in control performance which tends to be higher during the first 24h of tests with algae. We acknowledge the inconsistency in the report where on one the hand it is stated on page 82 that more information on transformation products is not necessary because the substance is				

shown to be rapidly biodegradable, while it is stated on page 92 that not all metabolites formed at >10% have been successfully identified. We consider MIT not rapidly degradable, since not all metabolites formed at >10% have been successfully identified. Therefore, it has not been convincingly demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment. In addition, large amounts of bound residues were observed in water-sediment studies. In our opinion this justifies chronic M factor 1 in a weight of evidence approach. We also note that in the CLH report for the C(M)IT MIT dossier, an additional degradation study carried out with MIT in sea water result in a DT50 of 29.7 days at 9°C (see comment FR).

RAC's response

RAC considers that the peculiar behaviour of the substance in the presence of algae shall be taken into account while evaluating the effectiveness of an ecotoxicological test and, if the usual 72h or 96h test duration are not fasible, "tests with a differing test duration could be used if no other acceptable data are available", as stated in the the Guidance on the application of CLP criteria (Version 4.1 – June 2015). RAC is aware that it is possible to decrease the normal duration of a growth inhibition test on algae to 48h length, if adequate justifications are provided and validity conditions are met. Anyway, the OECD guideline 201 and the ECHA guidance do not mention the possibility to adopt a 24h lenght for this test. In addition the validity criteria for the control performance (exponential control growth greater than a factor of 16) seems not be fulfilled in the first 24 h, in both acute and chronic test. Indeed the algal growth factor is 6.0 for acute test and 3.5 for the chronic one. On the other hand, due to the peculiar behaviour of the substance in presence of algae, the substance probably shows the strongest adverse effects in the first 24 hours.

RAC agrees with the DS evaluation regarding the biodegradation. The ready biodegradation studies show that MIT is not readily biodegradable. The primary biodegradation half-lives of MIT in the aquatic environment are very short, ranging from a couple of hours to a maximum of 4.17 days. However, not all metabolites detected at greater than 10% are definitively identified. Additionally, in the CLH report for the C(M)IT/MIT, an additional degradation study in seawater carried out on MIT results in a DT50 of 29.7 days at 9°C.

Consequently, MIT is considered not rapidly degradable for the purpose of classification and labelling.

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2015	Switzerland	Dow Europe GmbH	Company-Manufacturer	46

Comment received

We disagree with the M factor of 1 suggested for the chronic classification. Considering the rapid primary biodegradation of MIT evidenced in several environmental fate studies, and taking into account that the degradation products, which do not fullfill the criteria for classification as hazardous to the aquatic environment, can also be considered as rapidly biodegradable. In consequence, no M factor is required for MIT for chronic aquatic effects. See attachment.

ECHA note: The following attachment was provided with the comment above:

- *Dow comments to MIT CLH proposal*

Dossier Submitter's Response

We acknowledge the inconsistency in the report where on the one hand it is stated on page 82 that more information on transformation products is not necessary because the

substance is shown to be rapidly biodegradable, while it is stated on page 92 that not all metabolites formed at >10% have been successfully identified. We consider MIT not rapidly degradable, since not all metabolites formed at >10% have been successfully identified. Therefore, it has not been convincingly demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment. In addition, large amounts of bound residues were observed in water-sediment studies. In our opinion this justifies chronic M factor 1 in a weight of evidence approach. We also note that in the CLH report for the C(M)IT MIT dossier, an additional degradation study carried out with MIT in sea water result in a DT50 of 29.7 days at 9°C (see comment FR).

RAC's response

See answer to comment n. 45.

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2015	Germany	Henkel AG & Co. KGaA	Company-Downstream user	47

Comment received

We do not agree to the interpretation of the data provided in the CLH dossier and the resulting classification:

Biodegradation:
The conclusion „not rapidly biodegradable" according to CLP (1272/2008/EC) is not agreed. According to CLP Guidance a substance can be considered „rapidly degradable" if, among other, "…other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level > 70 % within a 28-day period." Thus, the degradation requirement will be fulfilled with an average degradation rate constant, k > -(ln 0.3 - ln 1)/28 = 0.043 day-1. This corresponds to a degradation half-life, t½ < ln 2/0.043 = 16 days. As shown in Table 18 and 19 a and b of the CLH report for 2-methylisothiazol-3(2H)-one half lives have been shown from different freshwater, estuarine and marine aquatic simulation tests at low substance concentrations were significantly below the half-life determined for substances considered to be readily biodegradable. The studies demonstrated a rapid biodegradation of the parent substance. One of the major metabolite, N-methyl malonamic acid (NMMA) and two other metabolites resulting from ring cleavage identified in simulation tests (N-(n-methyl) acetamide (NMA, sewage treatment plant study, MIT) and malonamic acid … are ready biodegradable and thus they will not be persistent in the aqueous phase, in the sediments or in the soil. The other metabolites will probably also expected to be quickly biodegraded in the environment, based on QSARs calculations (see also CLH report on C(M)IT/MIT). According to CLP Guidance II 2.3.1.(e) it is defined that "…ultimate degradation is determined i.e. … the individual degradation rates of the total biodegradation pathway." We believe that this has been proven by the respective experiments and the substance should be considered "rapidly biodegradable".

Ecotoxicity:
The chronic effects of 2-methylisothiazol-3(2H)-one are based on observations of an algae study at 24h. The normal duration of 72h of an algae study cannot be consulted because the substance is not stable. According to REACH guidance R.7b such evaluations can only be performed when the validity criteria of the controls are met. It cannot be seen why this criterion has not taken in consideration, although it was not in place at the time of the test. Since algae cells readily react with isothiazolinones evaluation of such tests is difficult. Nevertheless, due to its rapid dissipation from the test media it seems unlikely that algae

will be affected by the substance in the long term. Therefore, especially for the purpose of chronic classification it seems not feasible to use shorter exposure times of algae tests as provided in the CLH justification. This is also suggested in the report of p. 91.
The achievement of validity criteria in the first 24h of the test is also essential to conclude on the acute results of the algae test (ErC50). The test interpretation on the ecotoxicty of Pseudokirchneriella subcapitata (Hughes, 2004) is in our view not suitable for acute classification purposes.

Conclusion
According to the available data we suggest a classification H400, H411 (Ma-factor=1)

Dossier Submitter's Response

Biodegradation:
We consider MIT not rapidly degradable, since not all metabolites formed at >10% have been successfully identified. Therefore, it has not been convincingly demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment. In addition, large amounts of bound residues were observed in water-sediment studies. In our opinion this justifies chronic M factor 1 in a weight of evidence approach. We also note that in the CLH report for the C(M)IT MIT dossier, an additional degradation study carried out with MIT in sea water result in a DT50 of 29.7 days at 9°C (see comment FR).

Ecotoxicity:
We note that the acute classification is based on the *Skeletonema costatum* study which fulfilled the validity criteria for control performance also for the first 24 hours. We would further like to emphasize that we have given for chronic classification preference to EC10 endpoints to decide as these are derived from the dose-response curve and as such statistically more robust and less affected by variability in control performance. We agree that since algal cells readily react with isothiazolinones evaluation of such tests is difficult. For substances with such a specific mode of action on algae analytical measurents should preferable be performed at daily intervals (t=0, 24, 48 and 72 hours) as was done in an additional study in the case of DCOIT.

RAC's response

See answer to comment n. 45.

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2015	United Kingdom		MemberState	48

Comment received

UK Environment Agency comments:
Algae are the most sensitive species. Effects data in the CLH report are based on the most sensitive period during algal tests and results in some endpoints based on 24 or 48 hours. We note this method can be useful for assessment under the Biocides Regulation. However, for CLH we feel endpoints should reflect study conditions generating exponential growth in controls. OECD TG 201 highlights this can be 48 hours if a minimum multiplication factor of 16 is reached. It is not clear in this case if the algal endpoints reflect such validity criteria. If exponential growth was not observed in controls at 48 hours we feel algal endpoints should be based on time periods of exponential growth in controls, usually 72 or 96 hours. This allows for a consistent approach to characterise hazard in the environment for all

substances whereby effects are based on exponential growth. This is essential when determining chronic classification based on algal NOErC or EC10 values.

Given the above comments, we do not feel the data in the current CLH report are sufficient to determine M factors.

Dossier Submitter's Response

Growth curves demonstrated exponential growth of algae in the controls for 72 hours including the first 24 hours. We relied for classification on EC10 endpoints as these are derived from the dose-response curve and as such statistically more robust and less affected by variability in control performance which tends to be high during the first 24 hours in tests with algae.
The approach to deviate from standard 72h or 96h endpoints in is line with the CLH proposal for EC 55965-84-9 Reaction mass 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1) prepared by France and related to a specific mode of action on algae for isothiazolinones . Since algal cells readily react with isothiazolinones evaluation of such tests is difficult. For substances with such a specific mode of action on algae analytical measurents should preferable be performed at daily intervals (t=0, 24, 48 and 72 hours) as was done in an additional study in the case of DCOIT.

RAC's response

See answer to comment n. 45.

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	France		MemberState	49

Comment received

We agree with the conclusion on the environmental classification of MIT: H400 with M-factor =10 and H410 with M-factor =1

It seems however that the conclusions of the different section are not in good accordance with the conclusion:

P82 – It is concluded that more information on transformation products are not necessary because the substance is shown to be rapidly biodegradable. This is however not consistent with the chronic classification proposed on page 91, which implied that MIT is not considered as rapidly biodegradable. As mentioned on page 92, not all metabolites formed at >10% have been successfully and we therefore agree that MIT cannot be considered as rapidly biodegradable.
Additionally, please note that in the CLH report for the C(M)IT MIT dossier, an additional degradation study carried out with MIT in sea water result in a DT50 of 29.7 days at 9°C. Therefore we support that MIT should not be considered as rapidly biodegradable.

P89-91 - For each algae studies it is written that "For classification of chronic hazard the standard 72h NOEC is proposed as the endpoint should reflect effects over longer test duration rather than effects in the early phase of the exposure". However, 24 h ErC10 is then selected to determining the classification and we support this approach as it has been shown that ErC10 tends to increase with time because of the fast degradation of MIT in the algae tests. Could you please modify these sentences?

At last we have three minor comments:

P 77 – Water sediment study, Thor dossier, typo: Could you please add the number of the figure in the following sentence "The resulting common pathway for MIT and CIT is given in." P 80 - Simulation test: Sewage treatment plant, study by Rohm and Haas. We have the same study in the C(M)IT MIT dossier. Two values are available in the study for the amount of the applied activity in the effluent identified as MIT (12.2 and 11%). It has no consequences on environmental classification, but please note that we have reported the highest value in the CLH report for C(M)IT/MIT, as a worst case. P81 - Summary and discussion of degradation. Could you please add that abiotic degradation only occurs through photolysis?
Dossier Submitter's Response
P82 We apologize for the inconsistency in the report where on the hand it is stated on page 82 that more information on transformation products is not necessary because the substance is shown to be rapidly biodegradable, while it is stated on page 92 that not all metabolites formed at >10% have been successfully identified. We consider MIT not rapidly degradable, since not all metabolites formed at >10% have been successfully identified. Therefore, it has not been convincingly demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment. P89-91 Agreed. Sentence will be amended to "For classification of chronic hazard the standard 24 h ErC10 is proposed to determine the classification as it has been shown that ErC10 tends to increase with time because of the fast degradation of MIT in the algae tests." P77 We will add the number to the figure. P 80 Difference is noted. P81 Agreed, we will add that abiotic degradation only occurs through photolysis.
RAC's response
The comments are noted.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2015	Germany	Thor GmbH	Company-Manufacturer	50
Comment received				
CLH-Report, Chapter 1.3 p. 14 f Physical Hazards We do agree with the assigned physico-chemical properties, based on the available data.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
The comment is noted.				

ATTACHMENTS RECEIVED

NON-CONFIDENTIAL ATTACHMENTS

1. Abstracts of references, submitted on 24.08.2015 by the Finnish Institute of Occupational Health. *[Please refer to comment number 39]*

2. Dow comments to MIT CLH proposal, submitted by Dow Europe GmbH on 26.08.2015. *[Please refer to comments number 3, 19, 21]*

3. Statement of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe; DKG) concerning concentration limits for labelling of 2-methylisothiazol-3(2H)-one (MIT) in cosmetics and consumer products. Submitted by the German Contact Dermatitis Research Group(Deutsche Kontaktallergie-Gruppe; DKG) on 28.08.2015. *[Please refer to comment 10]*

4. Danish Comments to the CLH proposal for 2- methylisothiazol-3(2H)-one (MIT), (CAS no 2682-20-4). Submitted by Denmark on 28.08.2015. *[Please refer to comment 40]*

CONFIDENTIAL ATTACHMENTS

5. Yazar K., Lundov M.D., Faurschou A.,Matura M., Boman A., Johansen J.D. and Liden C., **Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study**. British Journal of Dermatology (2015) 173, pp115–122. Submitted by the Institute of Environmental Medicine, Karolinska Institutet on 27.08.2015. *[Please refer to comment number 5 and 32]*

6. Confidential attachment submitted by Thor GmbH on 27.08.2015 relating to the carcinogenicity endpoint. *[Please refer to comment 14]*

7. Image provided by an Individual *[Please refer to comments number 9 and 26]*