Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2*H*-isothiazol-3-one [EC no. 220-239-6] (3:1); Reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC no. 220-239-6] (3:1)

EC number: -

CAS number: 55965-84-9

CLH-O-0000001412-86-106/F

Adopted

10 March 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION MASS 5-CHLORO-2-METHYL-2H-ISOTHIAZOL-3-ONE AND 2-METHYL-2H-ISOTHIAZOL-3-ONE (3:1)

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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Chemical name: **Reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2*H*-isothiazol-3- one [EC no. 220-239-6] (3:1); Reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC no. 220-239-6] (3:1)**

EC number: -
CAS number: 55965-84-9
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	1
Comment received				
According to the statement on page 23 under the heading 4 C(M)IT/MIT is a mixture. However, classification can only be applied to substances and not to mixtures. Please provide a justification that this is a substance and not a mixture. On page 20, identified uses, only the use as biocidal product is mentioned. Additionally, C(M)IT/MIT is used as a preservative in various products, including cosmetics and paints. MSCA comments for Human Hazard only. • NL agrees with classification for skin corrosion with a specific concentration limit of ≥ 0.5% • NL agrees with classification as skin sensitizer Cat. 1A and retaining the specific concentration limit of ≥ 0.0015 % • NL asks for a clarification of the results of the respiratory sensitization study. Please consider applying EUH071 as the substance is classified for acute inhalation toxicity and the mechanism is shown to be corrosion.				
Dossier Submitter's Response				
C(M)IT/MIT is a substance which contains two components, the two components are not intentionally mixed, this is linked to the manufacturing process. The reaction leads to a mixture of C(M)IT and MIT with a ratio 3:1. Concerning the respiratory sensitization, due to lack of robust data, no conclusion can be				

drawn concerning the respiratory sensitisation properties of C(M)IT/MIT.
EUH071 could be envisaged based on the classification for acute inhalation toxicity and the corrosivity of the substance.

RAC's response

RAC concurs with the response provided by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Germany		MemberState	2

Comment received

1. We support with the proposal: Acute Tox.3/H301; Acute Tox.2/H330; Acute Tox.2/H310; Skin Corr 1C/H314: C ≥ 0.5%; Skin Sens 1A/H317: C ≥ 0.0015%
The following SCCS Opinion should be considered by RAC for this CLH proposal.
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_009.pdf

2. Substance identity:
It is not clear whether the Annex XV dossier and consequently the proposal for classification and labelling is for the "pure" CMIT/MIT (without solvent and additives) or for the stabilized substance. In the IUCLID file both identities are given and in the attached report contradictory information is given. For example in chapter 1.2.1 of the report it is stated "C(M)IT/MIT (3:1) is very reactive with some substances and should be stabilized in the product. That's why C(M)IT/MIT is produced in a continuous process directly at the product stage. Therefore the active substance is manufactured as a TK, in a solution with solvents and stabilizers. Different solvents and stabilizers exist. Most of the (eco)toxicological studies and all the physico-chemical properties have been performed with a solution of C(M)IT/MIT (3:1) at 14% in water with magnesium salts which is the product mostly on the market."
On the other hand in chapter 4 it is explained that "C(M)IT/MIT is a mixture. It is normally supplied as an aqueous solution of 14% C(M)IT/MIT (KathonTM886F or ACTICIDE 14). According to the definition of a "substance" under REACh, the proposed entry is referring to the "pure" C(M)IT/MIT with a purity expressed in dry weight also referred as active ingredient (a.i) in the document."
Thus, it has to be clarified whether the proposed classification is representative for the pure substance (without solvent and stabilizer) or for the substance including the stabilizer magnesium nitrate and magnesium chloride. In the first case the determined effects which were the basis for the classification proposal need to be representative only for CMIT/MIT – and not for the stabilizer. However, the stabilizer needs to be taken into account according to the CLP regulation when the substance is put on the market.
In case the substance including the stabilizers should be covered by this classification proposal all different solvents and stabilizer need to be taken into account. In case the different solvents and stabilizer lead to different classifications, different proposals need to be made.
Next to this no information about the physical chemical properties are given in the IUCLID file even though this information is given in the attached report. Therefore, to be consistent regarding the provided information within the IUCLID file and the CLP report it would be desirable to have all physico-chemical information in the IUCLID file, too.

3. Classification and labelling:
1.2 (Table 2): Concerning the third part of table 2 (Resulting harmonised …) we would like to remark that there should be a clear visible difference between the classification of the substance on the one hand and the specific concentration limits on the other hand.
1.3: Concerning the labelling proposal for the substance below table 3 we like to comment

as follows: Firstly the applicable pictograms (GHS06, GHS05, GHS09) are missing. Furthermore in our opinion the appropriate Hazard statements should be: H301, H310, H330, H314, H317 and H410.

Dossier Submitter's Response

2- Substance identity:
The classification presented in the CLH report is the classification of "pure" C(M)IT/MIT.

The tests tox are performed on the solution of 14% C(M)IT/MIT in water with magnesium salts. Therefore, as the proposed classification is an extrapolation from the 14% C(M)IT/MIT solution classification, the classification takes into account the stabilizers (magnesium nitrate and magnesium chloride) even if there are not part of the substance.

We have proposed this approach as C(M)IT/MIT have to be stabilized in the product and cannot be on the market whithout stabilizers.

We realised a toxicological assessement of the different biocidal sources submitted by the applicants and we concluded that all the provided sources with magnesium salts are covered by the tox tests carried out.

Other sources with different stabilizers and solvents were proposed in the biocidal dossier but they were not accepted because they were not covered by the toxicological studies.

Therefore, all the water based sources with magnesium salts are covered by this classification proposal.
For environmental classification, studies have been carried out with differents stabilisers which are not classified for environment and therefore they have no impact for classification of CMIT/MIT.

3- Classification and labelling: Indeed, the environment labelling should be only H410.

RAC's response

RAC concurs with the response provided by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2015	Netherlands	DSM Resins & Functional Materials	BehalfOfAnOrganisation	3

Comment received

Reference : ECHA Proposal for HCL of CMIT/MIT= 3:1 version number 2 dated April 15th 2015

Application of specific concentration limits - Skin corrosion & skin irritation

We have a question on the proposed specific concentration limits applicable to skin irritation as disclosed on page 5 of afore-mentioned document.

For the hazard class Skin Corr 1C - H314 (Causes severe skin burns and eye damage) the following specific concentration limit is proposed : $C \geq 0.5$ % w/w.

For the hazard classes Skin Irrit. 2 H315 (Causes skin irritation) and Eye irrit. 2 – H319 (Causes serious eye irritation) the following specific concentration limits are disclosed : $0.06 \leq C < 0.6$ % w/w.

Taking into consideration the specific concentration limit of C ≥ 0.5 % w/w applicable to hazard class Skin Corr 1C - H314, we would expect the following specific concentration limits applicable to hazard classes Skin Irrit. 2 H315 (Causes skin irritation) and Eye irrit. 2 – H319 : 0.06 ≤ C < 0.5 % w/w.
Dossier Submitter's Response
Agree, the specific concentration limits should be 0.06 ≤ C < 0.5 % w/w for Skin Irrit. 2 H315 and Eye irrit. 2 – H319.
RAC's response
RAC does not find the Dossier Submitter's proposal to amend the specific concentration limit well founded. The CLH report does not provide an assessment of the data previously reviewed by the Commission Working Group and, in the one rabbit study that informs on potency, a 0.5% solution of C(M)IT/MIT was irritating to skin, not corrosive. On this basis, RAC considers that there are insufficient data to change the SCLs from the existing values of 0.06 ≤ C < 0.6 % for Skin Irrit. 2; H315 and Eye Irrit. 2; H319.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	4
Comment received				
At the beginning of this section, it is stated that: 'Information from scientific literature is summarized here for information only in relation to the discussion on skin sensitization.' Only one study was selected that fulfilled this criterion. In the summary it is concluded that 'Based on these data from scientific literature, C(M)IT/MIT does not warrant classification for respiratory sensitisation. However, due to lack of robust data, no conclusion can be drawn concerning the respiratory sensitisation properties of C(M)IT/MIT.' In our opinion, it would be more correct to state that no data has been collected specifically considering respiratory sensitization, thus no conclusions can be drawn on either the endpoint or the availability of the data. In the summary of the study by Basketter et al, it is first stated that 'enhanced expression of cytokines associated with activation of T helper 1 (Th1) subset, including interferon-γ (IFN-γ) and interleukin 12 (IL-12) for skin allergen; activation of T helper 2 (Th2) subset, including enhanced expression of interleukin 4, 5, 10 and 13 (IL-4, IL-5, IL-10 and IL-13) for respiratory allergen.' However, in the results, it is concluded that 'C(M)IT/MIT induced production of low IL-10, IL-13, IL-5 and IL-4, and only low levels of IFN-γ in this experiment leading to the conclusion that C(M)IT/MIT presents a Th1-type response consistent with its skin sensitization properties'. Based on the interleukin types mentioned in the results, it would be more logical to assume a Th2 subset, also because there is no mention of IL-12. Please clarify why this conclusion was drawn. Also, cytokine profiling in the LLNA has not been validated to distinguish skin from respiratory sensitisers. Therefore, it would be better to delete this part to avoid confusion. An additional pulmonary hypersensitivity study was included in the latest SCCS opinion on CMI/MI (SCCS/1238/09). It concluded that 'Under the conditions of this study, CMI/MI				

induction at 4.8 mg ai/m3 did not result in an immediate or delayed pulmonary hypersensitivity response in guinea pigs when subsequently challenged with an aerosol of the test substance at 0.17, 0.35 and 0.72 mg ai/m3 nor CMI/MI did produce respiratory sensitisation. (Rohm and Haas Report No. 94RC-096 (1995). Kathon CG/ICP Biocide: Aerosol Pulmonary Hypersensitivity Study in Dunkin Hartley Guinea Pigs)'
Dossier Submitter's Response
Agree to add that no data has been collected specifically considering respiratory sensitization, thus no conclusions can be drawn on either the endpoint or the availability of the data. Agree to delete the part mentioned by NL to avoid confusion. The missed data could be added to the report.
RAC's response
Due to lack of available data for respiratory sensitisation, RAC agrees that no classification can be proposed for this endpoint.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Switzerland	Dow Europe GmbH	BehalfOfAnOrganisation	5
Comment received				
CMIT/MIT has been used for several decades in a multitude of industrial and consumer applications and in that time not a single case of clinically confirmed, respiratory allergy has been described in the open literature. In addition to this, mechanistic information provided in the dossier in the form of a summary of the study by Basketter et al clearly underlines that CMIT/MIT completely lacks potential for inducing Th2 type immune responses associated with respiratory allergy. We therefore do not agree with the dossier submitters speculative conclusions on this endpoint.				
Dossier Submitter's Response				
According to a comment from a member state, we will clarify this part to avoid confusion. No data has been collected specifically considering respiratory sensitization, thus no conclusions can be drawn on either the endpoint or the availability of the data.				
RAC's response				
Due to lack of available data for respiratory sensitisation, RAC agrees that no classification can be proposed for this endpoint.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	Germany	Thor GmbH, Landwehrstr. 1, 67346 Speyer	BehalfOfAnOrganisation	6
Comment received				
CLH-Report, Chapter 4.6.2.1 p. 56 We consider the scientific literature data are conclusive but not sufficient for classification for respiratory sensitization!				

Dossier Submitter's Response
No data has been collected specifically considering respiratory sensitization, thus no conclusions can be drawn on either the endpoint or the availability of the data.
RAC's response
These exposure-related issues are not relevant for classification and labelling proposals. Classification is based on the inherent hazardous properties of a substance.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Switzerland	Dow Europe GmbH	BehalfOfAnOrganisation	7
Comment received				
Proposal: Removal of Acute Tox. 2, H330 Fatal if inhaled We agree with the dossier submitters proposal that classification of CMIT/MIT for acute oral toxicity (Cat. 3) and acute dermal toxicity (Cat. 2) is appropriate. However we question the relevance of the acute inhalation classification given the effects observed were primarily due to the irritating/corrosive nature of the test material when exposed to an atmosphere to which workers would not generally be exposed. The vapour pressure of the active substance CMIT/MIT is extremely low and for inhalation testing requires generation of a forced atmosphere (aerosol) of certain measured mean respirable particle size. Under foreseeable use conditions, such atmospheres would never actually be generated. In addition, CMIT/MIT like all isothiazolones causes local, port of entry effects. Therefore, the over-riding cause of death in the acute inhalation study would be as a result of local irritation/corrosion of the respiratory tract. In obligate nasal breathers such as rats, the local effects result in asphyxiation caused by accumulation of exudates in the airways. This is apparent from the clinical signs (gasping, hyperpnea, expired nasal exudates) and macroscopic findings (congested lungs), observed during the study. Therefore, given classification and labelling is essentially concerned with warning users of the potential hazards associated with normal use of a substance, we feel the classification for acute inhalation toxicity is not warranted in the case of CMIT/MIT and should be removed.				
Dossier Submitter's Response				
The classification is based on intrinsic properties of the substance and is not linked to exposure considerations. The OECD guideline is designed with the same reasoning, it is stated that the substance has to be micronized (maybe with a size lower than that observed during exposure) in order to also assess its toxicity in alveolar part. The classification is based on hazards and does not take into account the exposure to the substance.				
RAC's response				
These exposure-related issues are not relevant for classification and labelling proposals. Classification is based on the inherent hazardous properties of a substance.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	Germany	Thor GmbH, Landwehrstr. 1, 67346 Speyer	BehalfOfAnOrganisation	8
Comment received				
CLH-Report, Chapter 4.2.1.2 p. 27 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, CMIT/MIT would be Cat. 2 for the inhalation acute toxicity. Applicant Thor questions 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 and contradictory inflation of labelling with GHS06 due to anticipation of aerosol exposures with corrosive materials.

CLH-Report, Chapter 4.2.1.3 p. 31 f
Dermal
Considering all available data suitable for classification, we do agree with the proposed classification for acute dermal. Following the cut off values in the most recent guidance on application of CLP criteria, CMIT/MIT would be Cat. 2 for the dermal acute toxicity.

Dossier Submitter's Response

The classification is based on intrinsic properties of the substance and is not linked to exposure considerations. The OECD guideline is designed with the same reasoning, it is stated that the substance has to be micronized (maybe with a size lower than that observed during exposure) in order to also assess its toxicity in alveolar part.
The classification is based on hazards and does not take into account the exposure to the substance.

RAC's response

These exposure-related issues are not relevant for classification and labelling proposals. Classification is based on the inherent hazardous properties of a substance.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	9

Comment received

NL agrees with classification for skin corrosion with a specific concentration limit of ≥ 0.5%. However, we doubt whether the available data allows a conclusion that the substance should be classified in subcategory 1C because this was based on the absence of corrosivity in a 1-hour study with a low concentration. Therefore, it cannot be excluded that testing higher concentrations would result in a different subcategory.
The proposed SCLs for skin and eye irritation of 0.6 to 0.06% (table 2) is not in line with the specific concentration limit of 0.5% for corrosion. Please adapt.

Dossier Submitter's Response

We propose a classification based on available data. We cannot propose a higher classification based on assumptions.

Agree, the specific concentration limits should be 0.06 ≤ C < 0.5 % w/w for Skin Irrit. 2 H315 and Eye irrit. 2 – H319.

RAC's response

RAC does not find the Dossier Submitter's proposal to amend the specific concentration limit well founded. The CLH report does not provide an assessment of the data previously reviewed by the Commission Working Group and, in the one rabbit study that informs on potency, a 0.5% solution of C(M)IT/MIT was irritating to skin, not corrosive. On this basis, RAC considers that there are insufficient data to change the SCLs from the existing values of 0.06 ≤ C < 0.6 % for Skin Irrit. 2; H315 and Eye Irrit. 2; H319.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Switzerland	Dow Europe GmbH	BehalfOfAnOrganisation	10

Comment received

Proposal: Skin Corr. 1C, H314 C ≥ 0.75%
We agree with the dossier submitters proposal to classify CMIT/MIT as Skin Corr. 1C, H314, however we believe additional classification for dermal and eye irritation is not warranted. According to the Guidance on the Application of the CLP Criteria section 3.2.2.6, substaces shall be labelled as corrosive or irritating and not both. In addition, the skin corrosion labelling and associated hazard statements would supercede the proposed H315 and H319. In addition, we propose the SCL for corrosivity be set at 0.75%. In the studies performed by Morrisson 1985, and described in tables 4.5-4 to 4.5-7, irreversible effects were seen at concentrations of 0.75% and 1.0%. At the SCL proposed of 0.5%, the DS concludes moderate irritation that was reversible at the end of the observation period was observed. According to the CLP regulation Article 10(1)
„Specific concentration limits and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance in another substance or in a mixture as an identified impurity, additive or individual constituent leads to the classification of the substance or mixture as hazardous.
Specific concentration limits shall be set by the manufacturer, importer or downstream user where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I."
The data presented clearly demonstrate the corrosive effects of CMIT/MIT are observed in guideline studies at 0.75% and above.
Overall we therefore propose the following labelling and concentration limits as appropriate for CMIT MIT: Skin Corr. 1C, H314 C ≥ 0.75%

Dossier Submitter's Response

We retained the lower concentration of 0.5% to be conservative regarding the severity of the effects.

RAC's response

RAC does not find the Dossier Submitter's proposal to amend the specific concentration limit well founded. The CLH report does not provide an assessment of the data previously reviewed by the Commission Working Group and, in the one rabbit study that informs on potency, a 0.5% solution of C(M)IT/MIT was irritating to skin, not corrosive. On this basis, although RAC concludes that the classification should be changed to Skin Corr. 1C, it considers that there are insufficient data to change the existing SCL (Skin Corr. 1C: C ≥ 0.6%).

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	Germany	Thor GmbH, Landwehrstr. 1, 67346 Speyer	BehalfOfAnOrganisation	11

Comment received

CLH-Report, chapter 4.5 p. 35 f
Skin corrosion
Considering all available data suitable for classification, we do agree with category 1C H314 being applied.
In the draft final CAR according to Doc IIA section 3.3 a classification as Skin Corr. 1C H

314: Causes severe skin burns and eye damage is required due to the study results. The specific concentration limit C ≥ 0.6%, according to the regulation 1272/2008/EC is proposed. Applicant Thor disagrees with the CLH report proposing a new specific concentration limit of 0.5%. Full reversibility of effects at 0.5% a.i. is observed 14-21 days after application (Dow study Morrisson, 1985). C(M)IT/MIT is corrosive to skin from a concentration of 0.75% a.i. The specific concentration limit of Skin Corr 1C, H314: C ≥ 0.6% is considered adequate and shall be maintained from DSD. CLH-Report, p.5. Skin Irritation Referring to the comments made, addressing skin corrosion (Chapter 4.5 p. 35 f). Full reversibility of effects at 0.5% a.i. is observed 14-21 days after application (Dow study Morrisson, 1985). C(M)IT/MIT is corrosive to skin from a concentration of 0.75% a.i. Consequently we disagree with the CLH report proposing a new specific concentration limit of < 0.5% for skin irritation. The specific concentration limit of Skin Irrit. 2 , H315: 0.06% ≤ C < 0.6% is considered adequate and shall be maintained.
Dossier Submitter's Response
We retained the lower concentration of 0.5% to be conservative regarding the severity of the effects of corrosion. The specific concentration limits should be 0.06 ≤ C < 0.5 % w/w for Skin Irrit. 2 H315 and Eye irrit. 2 – H319.
RAC's response
RAC does not find the Dossier Submitter's proposal to amend the specific concentration limit well founded. The CLH report does not provide an assessment of the data previously reviewed by the Commission Working Group and, in the one rabbit study that informs on potency, a 0.5% solution of C(M)IT/MIT was irritating to skin, not corrosive. On this basis, the data are not considered to be sufficient to justify changing the existing SCLs (resulting in classification as Skin Corr. 1C; H314: C ≥ 0.6%; Skin Irrit. 2; H315 and Eye Irrit. 2; H319: 0.06 ≤ C < 0.6%).

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Switzerland	Dow Europe GmbH	BehalfOfAnOrganisation	12
Comment received				
Please see above comment for Skin corrosion/irritation.				
Dossier Submitter's Response				
Please see above the answers.				
RAC's response				
Please see the above answers.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	Germany	Thor GmbH, Landwehrstr. 1, 67346 Speyer	BehalfOfAnOrganisation	13
Comment received				
CLH-Report, p. 5 Referring to the comments made, addressing skin corrosion (Chapter 4.5 p. 35 f). Full reversibility of effects at 0.5% a.i. is observed 14-21 days after application (Dow study Morrisson, 1985). C(M)IT/MIT is corrosive to skin from a concentration of 0.75% a.i. Consequently, we disagree with the CLH report proposing a new specific concentration limit of < 0.5%. The specific concentration limit of Eye Irrit. 2, H319: 0.06% ≤ C < 0.6% is considered adequate and shall be maintained.				
Dossier Submitter's Response				
We retained the lower concentration of 0.5% to be conservative regarding the severity of the effects.				
RAC's response				
RAC does not find the Dossier Submitter's proposal to amend the specific concentration limit well founded. The CLH report does not provide an assessment of the data previously reviewed by the Commission Working Group and, in the one rabbit study that informs on potency, a 0.5% solution of C(M)IT/MIT was irritating to skin, not corrosive. On this basis, RAC considers that there are insufficient data to change the existing SCLs (resulting in classification as Skin Corr. 1C; H314: C ≥ 0.6%; Skin Irrit. 2; H315 and Eye Irrit. 2; H319: 0.06 ≤ C < 0.6 %).				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Netherlands		MemberState	14
Comment received				
NL agrees with classification as skin sensitizer Cat. 1A and retaining the specific concentration limit of ≥ 0.0015 %. The EC3 value of approximately 30 to70 ppm (0.003 or 0.007%) in the LLNA studies would justify an SCL of 0.001% according to the CLP guidance.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Switzerland	Dow Europe GmbH	BehalfOfAnOrganisation	15
Comment received				
In section 3.4.2.2., the CLP Guidance describes in detail the approach of classification of a substance, the possibility for subcategorization (Category 1A or 1B) depending on fixed criteria and the setting of GCL/SCL's depending upon the potency of the substance as				

determined from animal models. We agree with the dossier submitter's proposal to subcategorize CMIT/MIT as Category 1A based on the available animal and human data. The existing SCL for CMIT/MIT of 0.0015% was established by the Commission Working Group in 2000. The conclusions drawn for establishing the SCL were largely based on evidence presented in the current classification and labelling proposal and the dossier submitter correctly states that there is no new evidence to warrant modification of the current SCL. A number of human repeat insult patch tests have been performed by Dow with CMIT/MIT in aqueous formulation i.e. to determine the intrinsic sensitizing potential of the active ingredient. When CMIT/MIT was applied at 100ppm (0.01%) and occluded for 24 hours, 1 of 101 volunteers reported as potentially sensitized. In a further study involving 14 volunteers treated daily for 3 weeks with 50ppm CMIT/MIT (0.005%), no reaction were observed in any of the subjects under study. Together, these studies indicate the induction concentration of CMIT/MIT to be >50ppm (0.005%). In addition to the Dow studies, HRIPT studies have been reported in the literature though several involved non-aqueous formulation of CMIT/MIT in consumer products. In summary, no signs of induction of skin sensitization were seen at CMIT/MIT levels under patch test conditions at concentrations below 12.5ppm (0.00125%). In aqueous formulation, the lowest concentration at which induction of sensitization was observed was 20 ppm (0.002%). In conclusion the available data in the open literature support the maintenance of the current SCL of 0.0015% especially given that the mode of exposure in HRIPT studies is exaggerated (24 hour continual exposure under occlusion) compared to real-world use scenarios. Anecdotal evidence in the form of prevalence rate data exists, which supports that 0.0015% is sufficiently protective for the hazard of sensitization, as observed by decreasing and subsequent stabilisation of trends in cases of allergic contact dermatitis in European clinical surveillance networks in the years following adoption of this concentration limit. In addition, given the advent of the 2nd ATP to CLP in 2015, the EUH 208 phrase will be required on all products containing CMIT/MIT above 1.5ppm (0.00015%) and will be further protective of individuals who may already be sensitized to CMIT/MIT.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Germany		MemberState	16
Comment received				
Skin Sensitisation: We agree with the proposed classification Skin Sens 1A/H317 based on the high potency in animals as shown by several guideline-conform studies and the high frequency of skin sensitisation in epidemiological studies. The LLNA study in CBA/J female mice (14) House R.V. Murine local lymph node assay with Chloromethylisothiazolinone and Methyliso-thiazolinone, 2000a, Covance Laboratories Study ID: 6228-145, Rohm and Haas Report N° 00RC-148A (November 7, 2000), Unpublished)demonstrated C(M)IT/MIT is sensitising at concentration ≥ 30 ppm a.i (or 0.003% a.i). In the absence of new information that could challenge the classification threshold value of 0.0015% a.i (15 ppm a.i) set during the Commission Working Group on the Classification and Labeling of Dangerous Substances in 2000, 15 ppm are regarded as SCL.				

Dossier Submitter's Response
Thank you.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Sweden		MemberState	17
Comment received				
The Swedish CA supports classification of C(M)IT/MIT (Cas No 55965-84-9) for skin sensitisation as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard class and the SCL.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	Germany	Thor GmbH, Landwehrstr. 1, 67346 Speyer	BehalfOfAnOrganisation	18
Comment received				
CLH-Report, Chapter 4.6 p. 42 f Considering all available data suitable for classification, we do agree with the conclusion and proposed classification with Skin Sens. 1A, H317; specific concentration limit: C < 0.0015% a.i.. We disagree with the CLH report regarding the following points: p. 53 We do consider the reference to cosmetic regulation and cosmetic use of C(M)IT/MIT not relevant in order to evaluate the technical uses and conduct classification and labeling. 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), [...]" Cosmetic use is ruled under a separate regulation with its own max. tolerable doses. And further, the CLH-report refers to potential leave on use concentrations for cosmetic purposes of 7.5 ppm. COMMISSION REGULATION (EU) No 1003/2014 of 18 September 2014) has banned leave on use for C(M)IT/MIT .This does mean any potential exposure from that side is only of hypothetical nature and not relevant any more. p. 53. We are missing in this section "human information" the reference to the human clinical data submitted with the BPD/BPR dossiers and also referred to in DocIIA , chapter 3.4. which is concluded by the eCA as followed: "A sensitisation HRIPT (Human Repeated Insult Patch Test) has also been conducted in human volunteers in the USA and indicates that the human threshold for skin sensitisation is probably at or above 357 ppm (corr. to 50 ppm a.i.or 0.005% a.i)"				

p. 54 Several literature references are cited in majority referring to cosmetic uses, reporting single cases and further more discussing other structurally related Isothiazolinones. The scientific data basis for C(M)IT/MIT is very broad and comprehensive. It should therefore be sufficient to make use of this data basis and to conclude on a labelling limit for skin sensitization based on the data available for C(M)IT/MIT.

It should also be noted, that the cosmetic literature does refer to single cases of pre-conditioned individuals. The data presented there are not obtained by investigating the general "healthy" public.

p. 55 (3rd paragraph, last sentence): " The reasoning to retain 15 ppm instead of 7.5 ppm is unknown and cannot be challenged in this dossier". This conclusion cannot be followed, based on the prior explanations given in this paragraph. The statements within this paragraph are not consistent.

We do agree with the CLH report regarding the following point:
p. 55 All available animal data do support a threshold for skin sensitisation of 30 ppm a.i.

Dossier Submitter's Response
The classification proposal is based on all available data and we consider that the effects observed even during cosmetic uses could be considered to support a weight of evidence approach.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2015	Germany		Individual	19
Comment received				
As a victim of MI and MCI I would like to give some comments. 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				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2015	Switzerland	Dow Europe GmbH	BehalfOfAnOrganisation	20
Comment received				
M factor for chronic aquatic classification based on non-rapidly degradable (M factor). Dow disagrees with the M factor of 100 suggested for the aquatic chronic classification, which is based on the assessment of CMIT/MIT being non-rapidly degradable. Experimental and QSAR evidence indicate that CMIT/MIT and their metabolites are rapidly degradable. CMIT/MIT is rapidly biodegradable Dow suggests aligning the conclusion of the classification with the evidence of rapid				

degradation presented in section 5.1.2.3 (Simulation studies). As outlined in section 5.1.3 (summary and discussion of degradation), biological half-lives in the environment are very short, ranging from a couple of hours to less than 6 days. CMIT/MIT is shown to be rapidly degraded via the biotic route to small polar compounds, which were rapidly biodegraded (section 5.1.2). The metabolism involves first the cleavage of the highly reactive N-S bond and subsequent oxidation. The mineralisation DT50 in the STP simulation studies were 0.36d for CMIT and 1.69 days for MIT. The rapid primary degradation and the mineralisation observed in the biodegradation simulation studies support the conclusion of rapid biodegradation, as indicated in section 4.1.2.9.2, 4.1.2.9.3 of the CLP. As summarised in section 6.1 the ecotoxicity testing of the metabolites do not fulfil the criteria for classification as hazardous to the aquatic environment. The experimental ecotoxicity testing demonstrates the loss of biocidal activity and reduced aquatic toxicity potential as a consequence of the cleavage of the isothiazolone ring, giving rise to transient metabolites having low environmental hazard.

Section 5.5 raised a concern regarding the non-extractable residues observed in the water/sediment simulation test. As indicated on page 90, it is assumed that biodegradation lead to the formation of ring-cleaved metabolites that formed tight association with sludge, sediment or soil matrix. This is an expected behaviour for such substances which react with nucleophilic functional groups of proteins, microbial cells, and organic matter present in natural aquatic sediment systems.

The non-extractable residues are a common factor in all soil and sediment studies with isothiazolones. The high NERs (non-extractable residues) would not be expected based on simple partitioning since the Kow and Koc values are not very high. Even with aggressive extraction solvents, the radioactivity can only be recovered by combustion. These results suggest covalent bonds are formed (likely between sulfur of the isothiazolone ring and reactive groups (thiols, amines) in the soil or sediment matrix. Based on the formation of covalent bonds with proteins, cells, and natural organic matter, the NER is expected to have low bioavailability and to be ultimately mineralized at the rate of natural organic matter decomposition. Testing of CMIT/MIT with three sediment-dwelling species, where residues of the applied CMIT/MIT were increasingly associated with sediment over the chronic exposure durations, the observed E/LC50 > 1 mg/kg and NOEC values > 0.1 mg/kg do not indicate significant ecological hazard potential of the NER residues of CMIT/MIT

We strongly disagree with the concluding sentence of section 5.5, which reverts back to QSAR prediction to conclude to the lack of rapid biodegradation, when the fate of CMIT/MIT was experimentally assessed in numerous fate studies.
Conclusion
Considering the rapid primary biodegradation of CMIT/MIT evidenced in several environmental fate studies, and that identified and predicted metabolites are expected to be rapidly degradable, the metabolites of CMIT/MIT do not fullfill the criteria for classification as hazardous to the aquatic environment (Section 4.1.2.9.3), CMIT/MIT can be considered as rapidly biodegradable. In consequence, an M factor of 10 for chronic aquatic effects is suggested.

Algal endpoints
Dow does not agree with interpretation of the effect on algal growth rate as stated in section 5.5.
Background:
The mode of action of the isothiazolinone biocides has been extensively researched (Williams, 2007). The biocidal effect is described as a two-step process involving rapid inhibition of growth and metabolism leading to a loss in viability of the cells. These effects

occur within minutes at the enzymatic level and can results in loss of viability within hours of exposure. The reaction of the biocides with biological cells is related to the loss of biocidal activity by opening the isothiazolone ring.
The applicant presents the reanalysis of the effect in line with the endpoints presented in the MIT studies. The effect concentrations inducing 10% and 50% inhibition of growth rate (ErC10 and ErC50), as well as the NOErC of all studies considered reliable by RMS France (reliability 1 and 2) are presented. The stability of the test material in the algal cultures will also be reviewed, as well as the initial cell density for comparative purposes of the ratio of concentration/cell density.
These studies include the following:
A7.4.1.3.a /01 (DOW) : Boeri R.L., Kowalski P.L., and Ward T.J. (1995a) Acute Toxicity of Kathon™ WT 14 % to the freshwater alga, Selenastrum capricornutum, TR Wilbury Study N° 658-RH, Rohm and Haas Report N° 95RC-0061 (August 2, 1995), Unpublished.

A7.4.1.3.b /03: (DOW) : Mixture of 5-Chloro-2-Methyl-4-Isothiazolin-3-One and 2-Methyl-4-Isothizaolin-3-One in a Ratio of 3:1: A 96-Hour Toxicity Test with the Marine Diatom (Skeletonema costatum), Palmer SJ; Cartee TL; Kendall TZ; Krueger, HO; Wildlife International, Ltd., 24 February 2011, DR-0303-2846-059.

Mode of action:
CMIT/MIT is a very effective biocide due to its rapid mode of action and its favorable environmental fate characteristics. CMIT/MIT utilizes a two-step mechanism involving rapid growth inhibition leading to a loss of viability. Growth inhibition is the result of rapid disruption of the central metabolic pathways of the cell by inhibition of dehydrogenase enzymes. Key physiological activities that are rapidly inhibited in microbial cells are growth (reproduction) and respiration (oxygen consumption and carbon dioxide production). These processes are critical in bacteria, algae, fungi, and invertebrates, which explains why CMIT/MIT is such a broad spectrum biocide.
CMIT/MIT rapidly associates with microbial [and similarly algal] cells. Inhibition of cellular activity is rapid (within minutes), whereas, cell death (cidal activity) is observed after several hours contact. Thus, the time course for efficacy is minutes to hours. Cell death results from the progressive loss of protein thiols in the cell from one of multiple pathways. As cell metabolism is disrupted, free radicals are known to be produced within cells and this is a likely contributor to the cidal mechanism. Overall, the higher the concentration of biocide, the shorter the contact time required for more complete kill.

Stability of the test concentrations in the algal study
In study A7.4.1.3.a /01 (DOW), the concentration in the test vessels were determined at study initiation and termination. The concentration in test vessels dosed at 19.7 µg ai/L initial measured concentration and lower was below the detection limit at 72hours.
In study A7.4.1.3.b /03, DOW, extensive analytical work was performed. Concentrations in exposed algal cultures were measured at 0, 24, 48, 72 hours in algal vessels. The stability of CMIT/MIT in saltwater algal medium in the absence in alga was confirmed in additional abiotic samples. In contrast, the concentration in test vessels dosed at 12 µg ai/L initial measured concentration and below could not be quantified (< LOQ) after 72hours. This finding is consistent with those of study A7.4.1.3.a /01 (DOW). The concentration of the three lowest test concentrations (0.84, 1.63 and 3.36 µg ai/L initial measured concentration) were below the limit of quantification after 24hours of exposures, supporting the rapid dissipation of the material driven by the reaction of the biocide with algal cells.
Initial cell density
The initial cell density was 10000 cells/mL in study A7.4.1.3.a /01 (DOW) and A7.4.1.3.b /03 (DOW), and 5000 to 10000 cells/mL in study A7.4.1.3-05 (Thor) thus at similar dose concentrations the ratio of cell density to CMIT/MIT concentration is assumed to be

comparable in the two studies from Dow and similar in the Thor study.
The studies were performed according to guidelines; however the freshwater algae were cultured under continuous illumination, while the marine algae were cultured in synchronous cultures (light/dark cycle of 16/8 h).

Analysis of the effects on alga

A7.4.1.3.a /01 (DOW) : Boeri R.L., Kowalski P.L., and Ward T.J. (1995a) Acute Toxicity of Kathon™ WT 14 % to the freshwater alga, Selenastrum capricornutum, TR Wilbury Study N° 658-RH, Rohm and Haas Report N° 95RC-0061 (August 2, 1995), Unpublished.

With respect to the validity criteria, the control cell density increased by 640x, which is acceptable. However, the coefficient of variation for overall growth was 13% (<7% is necessary to pass the criterion) and the section-by-section coefficient of variation was 42% (<35% is necessary to pass the criterion) which indicates a failure of both of these criteria.

Mean measured initial concentrations were used to calculate the EC values based on initial measured concentrations which are as follows (in µg/L):

Growth rate	EC50 (95% CI), µg/L	EC10 (95% CI) µg/L	NOEC, µg/L
0-24	13 (9.4-18)	8.6 (5.0-15)	9.9
0-48	18 (13-24)	8.4 (4.7-15)	9.9
0-72	27.00 (22-33)	13 (9.2-19)	9.9

Irrespective of the endpoints (ErC10, ErC50, NOErC) the effects on alga are equivalent or greater after 24 hours of exposure. The endpoints indicate limited recovery of the alga during the rest of the time course of the study.

A7.4.1.3.b /03: (DOW) : Mixture of 5-Chloro-2-Methyl-4-Isothiazolin-3-One and 2-Methyl-4-Isothizaolin-3-One in a Ratio of 3:1: A 96-Hour Toxicity Test with the Marine Diatom (Skeletonema costatum), Palmer SJ; Cartee TL; Kendall TZ; Krueger, HO; Wildlife International, Ltd., 24 February 2011, DR-0303-2846-059.

The study met the validity criterion of cell density increasing at least 16-fold throughout the study. Other validity criterions do not apply to testing on marine alga. The alga were cultured in synchronous cultures (light/dark cycle of 16/8 h), thus the division of cell should be observed every 24hours, but is strictly speaking not exponential.

Mean measured initial concentrations were used to calculate the EC values which are as follows (in µg/L; NC = not calculable):

Growth rate	EC50 (95% CI), µg/L	EC10 (95% CI) µg/L	NOEC, µg/L
0-24	>27 NC	**3.56** **(0.53-23.68)**	6.6
0-48	17.6 (15.5-20.0)	**8.83** **(6.5-11.9)**	1.6/6.6*

0-72	19.9 (18.5-21.5)	**8.67** **(7.06-10.62)**	 6.6

*The response is dose related for concentrations greater than 14 µg/L. Based on the lack of dose-response relationship at lower concentration, the relevant NOEC is 6.6 µg/L.

The ErC50 indicates constant effects after 48 and 72hours. The endpoints EC10 indicates effects slightly reducing over the time-course of the study: However the variability of the response at 24 hours was greater than observed in the freshwater tests. The NOEC is identical over the time course of the study. We re-iterate that the NOEC values were consistently determined at 6.6µg/L with the exception of the 48-hour time point. The significance of the effects at 3.4µg/L is indeed questionable, since there is a lack of dose-response relationship at concentration below 14µg/L and the growth rate at 6.6µg/L was not significantly different than that from the control. In consequence and based on the large confidence interval of the EC10 endpoint, the NOEC at 24hours of 6.6µg/L is suggested as a representative endpoint.

Summary
The applicants provide a rationale for the use of an alternative approach for the derivation of the toxicity endpoint of CMIT/MIT in algal tests. The use of the 24-hour measured CMIT/MIT concentrations to derive the toxicity endpoints is advocated based on the specific mode of action of CMIT/MIT in bacteria, fungi and algal cells and its rapid time course. The applicants disagree with the use of the 48 hour toxicity endpoints based on geometric mean concentration for the derivation of the toxicity endpoints and propose the following endpoints for classification

	ErC50 (24h)	Acute classification	Chronic (NOEC 24 h)	Chronic classification
Applicant proposal	0.013	Acute 1 M =10	0.0066	Chronic 1 M=1

Dossier Submitter's Response

Biodegradability of C(M)IT/MIT

We agree that for several simulation degradation studies, DT50 for primary degradation is below 16 days and resulting metabolites have been shown to be either readily biodegradable or transient and that same metabolites are expected to be less toxic than the parent substance C(M)IT/MIT. Nevertheless, in marine water, a DT50 for primary degradation >16 days is observed for the highest tested concentration (100 µg/L) and it can therefore not been considered that C(M)IT/MIT is rapidly biodegradable. Besides it is true that very short half life have been reported in the STP simulation studies. However, according to Guidance on the Application of the CLP Criteria (version 4.1, june 2015) results from such tests cannot be used for the classification as the microbial biomass in STP is significantly different from the biomass in the environment.
NER and QSAR results have only been provided in the CLH report in a weight of evidence approach. Regarding NER, it should be kept in mind that the bound residues issue is not clearly elucidated in the guidelines and the long term bioavailability of NER is still questionable. No sediment threshold toxicity values have yet been defined for the toxicity on sediment dwelling organisms; nevertheless please note that for Lumbricus variegatus a EC50<1 mg/kg has been derived. At last, even if experimental studies are often preferred to QSAR data, it is only underlined in the CLH report that in the case of C(M)IT/ MIT, QSAR supports experimental studies indicating that neither C(M)IT nor MIT are readily biodegradable.

Algal endpoints

A7.4.1.3.a /01 (DOW): we agree with the analysis of the effects on alga proposed by Dow Europe GmbH. Indeed the most sensitive of this period is 24 hours and in this case it is relevant to provide endpoints as initial measured concentrations. Please however note that we do not understand the validity criteria mentioned in the comment by Dow. Validity criteria, which have been determined for each section in the CLH report, are reported in the following table:

	Cell density increasing factor	Coefficient of variation for section-by-section specific growth rates	coefficient of variation of average specific growth rates during the whole test period
24h	2.5	43%	N.A.
48h	12	12%	10%
72h	64	20%	2%

According to this table, it is questionable if endpoints derived at 24 hours can be considered as chronic endpoints. Nevertheless, as the tested marine algae is more sensitive than the freshwater algae in this test, this study has not been selected to compare the endpoint to classification thresholds.

A7.4.1.3.b /03, DOW: we disagree with several points of comments provided by Dow Europe GmbH.

First, it has been agreed, in the framework of Biocidal Product Regulation, that the effect observed at 3.4 µg/L at 48 hours should be considered as significant. Therefore the NOEC at 48h is 1.6 µg/L and 48h has been considered as the most sensitive period of this test, which is supported by the EC50 (17.5 µg/L, based on initial measured concentrations), which is also the lowest at 48h. Additionally, as a multiplication factor of 55 is reported after 48h for the cell density in controls, study conditions generating exponential growth are confirmed. The NOEC endpoint derived at 48h is therefore relevant for the chronic classification. Besides, because of the fast dissipation of the active substance (see table 1) and as measured concentrations are available, it appears reasonable to choose endpoints based on mean measured concentrations (see table 2). Thus, NOE_rC 48h (0.49 µg a.i./L) and E_rC50 48h (5.2 µg/L) have been selected for the comparison to classification endpoints.

Table 1: measured concentration of C(M)IT/MIT in the test

Dose levels (µg ai/L)	measured at 0h, µg ai/L	measured at 24h, µg ai/L	measured at 48h, µg ai/L	measured at 72h, µg ai/L
0	<0,3*	<0,35**	<0,3*	<0,3*
0.75	0.824	0.0711	0.018	<0,3*
1.5	1.63	0.168	0.0355	<0,3*
3	3.36	0.325	0.069	<0,3*
6	6.59	1.05	0.215	<0,3*
12	13.5	3.33	0.817	<0,3*
24	26.9	18	10.2	5.72

*LOQ = 0.3 µg ai/L at 0, 48, 72 and 96h

**LOQ = 0.35 µg ai/L

Table 2: mean measured concentration of C(M)IT/MIT in the test based on initial concentration and on concentration measured at the considered time

	Geometric mean based on initial concentration and on concentration measured at the considered time (µg ai/L)*		
Dose levels (µg ai/L)	24h	48h	72h
0	0.16	0.15	0.15
0.75	0.35	0.35	0.35
1.5	0.52	0.49	0.49
3	1.04	0.71	0.71
6	2.63	1.19	0.99
12	6.70	3.32	1.42
24	22.00	16.56	12.40

*LOQ/2 has been considered for each measured concentrations which were below LOQ

RAC's response

RAC agrees with the DS evaluation regarding the biodegradation, in particular that there is a reliable simulation study in marine water resulting in a DT_{50} value for primary degradation >16 days. Therefore C(M)IT/MIT cannot be considered rapidly degradable. Moreover, according to Guidance on the Application of the CLP Criteria results from STP studies cannot be used for the classification as the microbial biomass in STP is significantly different from the biomass in the environment.

Regarding the ecotoxicogical studies, due to the peculiar behaviour of the substance in presence of the algae, the most sensitive period of the test is within the first 48h. The OECD TG 201 guidance allows a 48h test period if the unlimited, exponential growth is maintained during the test as long as the minimum multiplication factor of 16 is reached. Since this requirement is fulfilled, with a multiplication factor of 55, RAC considers the 48h value of the marine algae *Skeletonema costatum* test useful for classification.
Moreover RAC supports the DS proposal for a 48h NOEC of 0.49 µg/L, assuming as significant the observed effect at 3.4 µg/L.

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2015	Germany	Henkel AG & CO. KGaA	BehalfOfAnOrganisation	21

Comment received

We do not agree to the interpretation of the data provided in the CLH Report and 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 5.1-1 of the CLH report for the Reaction mass 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1) 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. In addition the report states that "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 section 4.3)". 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 Reaction mass 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1) are based on observations of an algae study at 48h (Skeletonema costatum, Palmer et al 2009). The normal duration of 72-96h of an algae study was not 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. From the CLH report it cannot be seen if this criterion has taken in consideration. 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 reaction mass in the long term. Therefore, especially for the purpose of classification and labelling it seems not feasible to use shorter exposure times of algae tests as provided in the CLH justification.
The achievement of validity criteria in the first 48h of the algae test, is also essential to conclude on the acute ecotoxicity against algae (ErC50). Therefore, the test interpretation on the ecotoxicty of Skeletonema costatum (Palmer et al, 2009) must be further assessed for a final interpretation of acute classification purposes. In addition we propose to evaluate a weight of evidence approach (acc. CLP guidance The second acute ecotoxicity data in this range for the marine copepod Acartia tonsa (Weideborg, 1995) shall be evaluated in the light of its reliability and significance by the weight of evidence (CLP Guidance 4.1.3.2.4.), since this result seem not match with other available data for invertebrates. Considering the above statements on acute ecotoxicity a Ma-factor of 10 could result (need to be further assessed).

Conclusion
According to the available data we suggest a classification H400, H410 (Ma-Factor 10*; Mc=1)
*Ma-factor should be further evaluated by weight of evidence

Dossier Submitter's Response

Biodegradability of C(M)IT/MIT
We agree that for several simulation degradation studies, DT50 for primary degradation is below 16 days and resulting metabolites have been shown to be either readily biodegradable or transient and that same metabolites are expected to be less toxic than the parent substance C(M)IT/MIT. Nevertheless, in marine water a DT50 for primay degradation >16 days is observed for the highest tested concentration (100 µg/L) and it can therefore not been considered that C(M)IT/MIT is rapidly biodegradable. Besides it is true that very short half life have been reported in the STP simulation studies. However, according to Guidance on the Application of the CLP Criteria (version 4.1, June 2015) results from such tests cannot be used for the classification as the microbial biomass in STP is significantly

different from the biomass in the environment.

Ecotoxicity:
Validity criteria of the algae study (*Skeletonema costatum*, Palmer et al 2009) are fulfilled at 48h :

- cell density increasing factor (>16) : 55
- coefficient of variation for section-by-section specific growth rates (<35%) : 13%
- coefficient of variation of average specific growth rates during the whole test period (<10%) : 2%

Additionally, as a multiplication factor of 55 is reported after 48h for the cell density in controls, study conditions generating exponential growth are confirmed. The endpoints derived at 48h are therefore relevant for the chronic classification.
Please note as validity criteria are fulfilled at 48h, EC50 48h is still reliable and there is therefore no need to provide more information here on the validity of the study carried out with *Acartia tonsa*

RAC's response

See answer to the comment 20.

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	Germany	Thor GmbH, Landwehrstr. 1, 67346 Speyer	BehalfOfAnOrganisation	22

Comment received

CLH-Report, Chapter 5.4, p. 94 f.
"Table 5.4-1: Summary of relevant information on aquatic toxicity"
The values presented for the algae studies in Table 5.4-1 should all be harmonized to 72 h.

CLH-Report, Chapter 5.5, p. 99 f
Aquatic Acute 1. M-factor=100
The environmental classification in the CLH-dossier is based on the 48 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.

CLH-Report, Chapter 5.5, p. 99 f
Aquatic Acute 1. M-factor=100
The study by Palmer et al. (2009) shows an ErC50 after 72 h >0.01 mg/L, so triggering an acute M-factor of 10. We therefore believe that based on the existing aquatic toxicity data, the acute M-factor for C(M)IT/MIT should be 10 and not 100.

CLH-Report, Chapter 5.5, p. 99 f
Aquatic Chronic 1, H410. M-factor=100
The environmental classification in the CLH-dossier is based on the 48 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.

CLH-Report, Chapter 5.5, p. 99 f
Aquatic Chronic 1. M-factor=100

Thor assumes that the Aquatic chronic M-factor is allocated on the basis of the new

interpretation of the marine water algae test (using the NOEC value derived after 48 h) and the fact that C(M)IT/MIT is not considered as rapidly biodegradable.
Thor does not agree to this view presented in the CLH opinion. C(M)IT/MIT should be regarded as rapidly biodegradable for several reasons.
a) It is stated in the CLH-dossier for the substance MIT (CAS-No. 2682-20-4) that MIT can be regarded as rapidly biodegradable because its degradation products are rapidly biodegradable and less toxic than the parent compound. MIT is in our understanding the relevant compound of the reaction mass C(M)IT/MIT regarding biodegradability. It is therefore not comprehensible that C(M)IT/MIT should be regarded as not rapidly biodegradable.
b) The evaluating competent authority for C(M)IT/MIT under the BPR, France, wrote in the draft final CAR for C(M)IT/MIT (Doc IIA_CMIT-MIT_all PTs, Chapter 1.5.2, p. 40): "ECHA should decide whether C(M)IT/MIT is ready biodegradable or not."
c) France also wrote during the commenting phase prior to the WG meeting in March 2014 (RMS responses to comments on the draft Competent Authority Report of CMIT/MIT (PT 6)-Thor (10.03.2014), Comment 22 and 23, p. 13 f.):"For CLP classification, CMIT/MIT will be considered as rapidly degradable and then the proposed classification is H400 with M-factor 10 and H410 with M-factor =10.". The data basis on which this conclusion was drawn has not changed since that date.
d) Thor does not agree that the results from the OECD 301 D study on ready biodegradability are not considered relevant because of the activated sludge used. The material used in the study is in our understanding suitable according to the guideline ("predominantly domestic sewage") as the sewage treatment plant where the material originates mainly treats domestic waste. We therefore consider C(M)IT/MIT to be ready and thus also rapidly biodegradable.
Thus, when summarizing all these facts we propose to change the chronic M-Factor to 10.

Dossier Submitter's Response

Ecotoxicity data

In each algae tests, because of the fast dissipation of C(M)IT/ MIT, it has been considered relevant to derive the toxicity endpoint for the most sensitive period of the test. For the study A7.4.1.3.a /01 (DOW), 24 hours has been considered as the most sensitive period as endpoints were higher for further test duration. However, because of a low multification factor in the control at 24 hours, endpoints derived at 24 hours cannot be considered as chronic endpoints. Nevertheless, as the tested marine algae is more sensitive than the freshwater algae in this test, this study has not been selected to compare the endpoint to classification criteria.

In the study with the marine algae (A7.4.1.3.b /03, DOW) multiplication factor of 55 is reported after 48h for the cell density in controls which supports study conditions generating exponential growth. The endpoints derived at 48h are therefore relevant for the chronic classification. As the lowest endpoints in this study is observed at 48h and as the NOEC is the lowest endpoint of aquatic toxicity test, NOE_rC 48h (0.49 µg a.i./L) has been selected for the comparison to classification endpoints. Besides, as all validity criteria are fulfilled at 48 hours and as the lowest EC50 is also observed at 48 hours, it is relevant to base the acute toxicity on this EC50 derived at 48 hours.

Biodegradability of C(M)IT/MIT

a) No clear conclusion dealing with the rapid biodegradation of MIT are presented in the CLH report of this substance. Indeed in the conclusion, it is indicated that definitive identification of all metabolites >10% in aquatic biodegradation studies is required to justify a non chronic classification of MIT. Besides a chronic M factor of 1 is selected which correspond to a non-rapidly biodegradable substance according to the selected

ErC10.

b) And c) We should admit that in a first assessment we believed that enough information had been brought to consider C(M)IT/MIT as rapidly biodegradable. However, after a carefull review of available data, including marine degradation data, we have considered that C(M)IT/MIT should be considered as non-rapidly biodegradable and this conclusion has been reported in the final version of the biocide assessment report. As the interpretation of the data can be controversial, it has been indeed indicated in the biocide assessment report that this issue should be confirmed during the CLH report discussions.

d) In the MIT dossier, MIT has not been considered as readily biodegradable. Moreoever, when tested separately, C(M)IT has been shown to be readily biodegradable with a failure of the 10-day window at the lowest concentration tested (0.03 mg/L), and not readily biodegradable at the two other tested concentrations (0.1 and 0.3 mg/L), whereas MIT was not readily biodegradable whatever the tested concentrations (0.01-0.1 mg/L, 48-56% of degradation at 28 days). No toxicity test was carried out in these studies, nevertheless monitoring of microbial density supported a toxic effect on microoganisms at the highest tested concentration for C(M)IT and at all tested concentrations for MIT. Besides, in the study that you mention, the test has been carried out with an inoculum from STP receiving both domestic wastewater and chemical wastes and really higher concentrations have been used (4.2 mg/L C(M)IT and 1.4 mg/L MIT in the same test). Despite of these high concentrations, no toxicity occurred in this test, as the ready biodegradation threshold was achieved within 7 days, and it is therefore strongly suspected that inoculum was adapted. In this case, it can not been considered according to this test that C(M)IT/MIT is readily biodegradable.

RAC's response

See answer to the comment 20.

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2015	United Kingdom		MemberState	23

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

A multiplication factor of 55 is reported after 48h for the cell density in controls which supports study conditions generating exponential growth. The endpoints derived at 48h are therefore relevant for the chronic classification.

RAC's response
Due to the peculiar behaviour of the substance in presence of the algae, the most sensitive period of the test is within the first 48h. The OECD TG 201 guidance allows a 48h test period if the unlimited, exponential growth is maintained during the test as long as the minimum multiplication factor of 16 is reached. Since this requirement is fulfilled, with a multiplication factor of 55, RAC considers the 48h value of the marine algae *Skeletonema costatum* test useful for classification.