Committee for Risk Assessment

RAC

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

10 March 2016

CLH-O-0000001412-86-106/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

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**

The proposal was submitted by **France** and received by the RAC on **16 April 2015**.

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS). The classification notation for 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **9 July 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **24 August 2015.**

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Andrew Smith**

Co-rapporteurs, appointed by RAC: **Pietro Paris**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation; the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling of the substance specified above was reached on **10 March 2016** and was adopted by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

Annex VI	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Entry	613-167-00-5	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)	-	55965-84-9	Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 3 * Skin Corr. 1B Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H331 H311 H301 H314 H317 H400 H410	GHS06 GHS05 GHS09 Dgr	H331 H311 H301 H314 H317 H410		Skin Corr. 1B; H314: C ≥ 0,6 % Skin Irrit. 2; H315: 0,06 % ≤ C < 0,6 % Eye Irrit. 2; H319: 0,06 % ≤ C < 0,6 % Skin Sens. 1; H317: C ≥ 0,0015 %	
Dossier submitter proposal	613-167-00-5		-	55965-84-9	Acute Tox. 2 Acute Tox. 2 Acute Tox. 3 Skin Corr. 1C Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	H330 H310 H301 H314 H317 H400 H410	GHS06 GHS05 GHS09 Dgr	H330 H310 H301 H314 H317 H410	EUH071	Skin Corr. 1C; H314: C ≥ 0,5 % Skin Irrit. 2; H315: 0,06 % ≤ C < 0,5 % Eye Irrit. 2; H319: 0,06 % ≤ C < 0,6 % Skin Sens. 1; H317: C ≥ 0,0015 % M=100 M=100	
RAC opinion	613-167-00-5		-	55965-84-9	Acute Tox. 2 Acute Tox. 2 Acute Tox. 3 Skin Corr. 1C Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	H330 H310 H301 H314 H317 H400 H410	GHS06 GHS05 GHS09 Dgr	H330 H310 H301 H314 H317 H410	EUH071	Skin Corr. 1C; H314: C ≥ 0,6 % Skin Irrit. 2; H315: 0,06 % ≤ C < 0,6 % Eye Irrit. 2; H319: 0,06 % ≤ C < 0,6 % Skin Sens. 1A; H317: C ≥ 0,0015 M=100 M=100	
Resulting Entry	613-167-00-5		-	55965-84-9	Acute Tox. 2 Acute Tox. 2 Acute Tox. 3 Skin Corr. 1C Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	H330 H310 H301 H314 H317 H400 H410	GHS06 GHS05 GHS09 Dgr	H301 H310 H330 H314 H317 H410	EUH071	Skin Corr. 1C; H314: C ≥ 0,6 % Skin Irrit. 2; H315: 0,06 % ≤ C < 0,6 % Eye Irrit. 2; H319: 0,06 % ≤ C < 0,6 % Skin Sens. 1A; H317: C ≥ 0,0015 M=100 M=100	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

This substance is a reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one in the ratio 3:1 (further referred to as **C(M)IT/MIT**). It is manufactured as a technical concentrate and produced in a solution with solvents and stabilisers. The majority of toxicity studies summarised in the CLH report have been performed on a specific aqueous formulation which contains around 14% of the 3:1 reaction mass. The SCSS opinion on C(M)IT/MIT (SCCS/1238/09) noted that the biocide is produced by an integrated production process (reaction mass), resulting in an approximate total of 14% active ingredients, 16% magnesium nitrate, 10% magnesium chloride and 62% water. However, the Biocidal Product Committee also mentioned that the theoretical (calculated) dry weight specification-minimum purity of C(M)IT-MIT (3:1) at 579 g/kg i.e. 60% w/w (BPC, 2015). Some manufacturers also report active ingredients of 14% w/w minimum on their website. Finally, Industry could not confirm whether it was possible to produce the substance at > 14%. In view of this uncertainty, RAC queried whether the concentration of 14% should be specified in the Annex VI entry for this substance. In order not to restrict the entry in Annex VI of CLP to a concentration of 14% while considering that more diluted forms may be available to workers or professionals, no specification of the maximum concentration of the active ingredient C(M)IT/MIT is proposed. This approach is also in line with all entries of active substances in CLP. This reaction mass will be referred in the opinion as "C(M)IT/MIT".

Germ cell mutagenicity, carcinogenicity, reproductive toxicity and aspiration toxicity were not considered in this dossier; hence RAC has not evaluated these hazard classes.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) did not propose classification for physical hazards. The data on physico-chemical properties did not indicate any concerns and as such, C(M)IT/MIT does not meet the criteria for classification. According to the assessment of the DS, C(M)IT/MIT was not explosive in a standard study (EC method A.14) and a test using EC method A.10 showed that C(M)IT/MIT was not highly flammable. Examination of the chemical structure indicated that C(M)IT/MIT would not have any oxidising properties, therefore C(M)IT/MIT does not meet the criteria for classification as an oxidising substance.

Comments received during public consultation

No comments were received regarding this endpoint.

Assessment and comparison with the classification criteria

RAC is in agreement with the DS that **classification is not required for physico-chemical hazards.**

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The DS proposed to remove the existing minimum classification for acute toxicity of C(M)IT/MIT by the oral route (Acute Tox. 3*; H301). In the two acute oral toxicity studies available (of which one was performed according the OECD Test Guideline (TG) 401), the oral LD_{50} in rats were 457 and 472 mg/kg bw, corresponding to 64 and 66 mg a.i./kg bw, respectively. These values lie within the range 50-300 mg/kg for classification as Acute Toxicity 3 (H301: Toxic if swallowed) under CLP.

Following inhalation exposure (nose-only, 4 h), the LC_{50} of C(M)IT/MIT in rats ranged from 0.169-0.33 mg/L air and the effects observed were consistent with respiratory irritation. These values lie within the range of 0.05 – 0.5 mg/L for classification with Acute Toxicity 2 (H330: Fatal if inhaled).

After dermal exposure, the LD_{50} of C(M)IT/MIT in rats was 141 mg/kg bw. In rabbits, the LD_{50} was determined to be 87.12 mg/kg bw. These values both lie within the range of 50-200 mg/kg bw and so meet the classification criteria for Acute Toxicity 2 (H310: Fatal by contact with skin).

The DS concluded that C(M)IT/MIT is highly toxic by the dermal and inhalation routes, inducing effects consistent with its corrosive properties.

Comments received during public consultation

Two industry stakeholders and one MS agreed with the proposed category 2 classification for acute dermal toxicity. The same MS also agreed with the proposal for acute inhalation toxicity category 2.

One of the stakeholder organisation agreed with acute oral toxicity category 3 but questioned the appropriateness of the proposed classification for acute inhalation toxicity. The low vapour pressure of C(M)IT/ MIT required generation of an aerosol. Such an atmosphere is unlikely to be generated under foreseeable conditions. Furthermore, the observed effects were considered to be primarily due to the irritating/ corrosive nature of the test material.

The other industry stakeholders agreed with the proposed classification for acute inhalation toxicity (category 2) but did question the relevance of data obtained by means of an aerosol in view of the low vapour pressure of the substance.

In response, the DS explained that these exposure-related issues are not considered for classification. The proposal is based on the relevant criteria, which are based on the inherent hazardous properties of substance concerned.

One MS suggested applying the phrase EUH071 (Corrosive to the respiratory tract), making the case that this could be justified by the corrosive nature of C(M)IT to skin and the evidence from acute studies of toxicity via inhalation. The DS replied that EUH071 could be envisaged based on the classification for acute inhalation toxicity and the corrosivity of the substance.

Assessment and comparison with the classification criteria

Oral

Two acute oral toxicity studies in SD rats provide were considered acceptable and reliable although one study was conducted prior to OECD TG 404 and GLP. In both studies, diluted products containing 13.3 to 14% C(M)IT/MIT in aqueous solutions were administered as a single dose, followed by a clinical observation period of 14 days. Both studies provided very similar LD_{50} and the clinical signs were consistent with the corrosive properties of C(M)IT/MIT (see below). No gender difference was apparent. The oral LD_{50} in rats ranged between 64 (males only) and 66 (males and females combined) mg C(M)IT/MIT kg bw.

In conclusion, RAC agrees with the DS to remove the minimum classification for C(M)IT/MIT since oral LD_{50} values in rats lie within the range (50-300 mg/kg bw) for classification as Acute Tox. 3 (H301: Toxic if swallowed) under CLP.

Dermal

Two dermal studies are available, one in rats and one in rabbits.

The study in rats was carried out according to OECD TG 402 and GLP. In this study, male and female rats were exposed to an aqueous solution of C(M)IT/MIT (14%) i.e. a dose level of 141 mg C(M)IT/MIT/kg bw for 24 h. At this single dose level there was 30% mortality and so the LD_{50} was determined to be > 141 mg/kg bw.

A study in rabbits was also available, carried out in 1976 prior to OECD guidelines and GLP. In this study male rabbits were exposed to an aqueous solution of C(M)IT/MIT (14%) at doses of 313, 625, 1250 and 2500 mg test material/kg bw for 24 h. The LD_{50} was determined to be 87.12 mg C(M)IT/MIT/kg bw. This finding is in accordance with the criteria for classification with acute dermal toxicity category 2 ($50 < LD_{50} \leq 200$ mg/kg bw).

Inhalation

Two acute toxicity experiments via the inhalation route are available. Both of these studies were carried out according to OECD TG 403 and in compliance to GLP.

In both studies, male and female rats were exposed to an aerosol generated from an aqueous solution of C(M)IT/MIT (14%), nose-only, for 4 h. In the first study, the mean respirable fraction (< 7 µm) was 57 ± 9% and the combined LC_{50} for males and females was 0.33 mg/L C(M)IT/MIT. In the second study, the mean respirable fraction (< 7 µm) was 85-95.7% and the combined LC_{50} for males and females was 0.171 mg/L C(M)IT/MIT. In both studies, particle size in the test atmosphere achieved the recommended aerodynamic diameter standard of 1-4 µm.

The LC_{50} values of 0.33 and 0.171 mg/L are both within the range ($0.05 < LC_{50} \leq 0.5$ mg/L) given in the criteria for classification in Acute Inhalation Toxicity Category 2 for dusts and mists.

An industry stakeholder queried the validity of using data from studies that involved the generation of an aerosol of C(M)IT/MIT claiming that such exposure conditions would not be generated under foreseen conditions. However, RAC agrees with the response of the DS that the classification should be based on the inherent properties of C(M)IT/MIT and therefore the data should be taken into account.

One MS and the DS considered that EUH071 ("corrosive to the respiratory tract") may also be applicable to C(M)IT/MIT. According to Annex II of the CLP Regulation, EUH071 "shall be assigned for substances and mixtures in addition to classification for inhalation toxicity, if data are available that indicate that the mechanism of toxicity is corrosivity". The findings in the rat acute inhalation studies indicate that the lethality observed is likely to have been due to severe local irritation or corrosion: gasping, rales, hyperpnea, dyspnoea and exaggerated respiratory movements observed immediately after exposure, also congested lungs and gas-filled stomachs and/or intestines at necropsy. This latter effect was deemed to be the result of swallowing of air in an attempt to breathe. The clinical signs disappeared in all surviving animals, taking at most from 6 to 12 days to resolve.

Given that C(M)IT/MIT is corrosive to the skin and eyes (see below), RAC considers the most likely explanation for the observed inhalation toxicity is its corrosive nature. On this basis, although the DS and those who responded during the public consultation did not consider the potential for other mechanisms of toxicity, RAC concludes using expert judgement that EUH071 should be applied.

In conclusion, RAC agrees with the DS that classification of C(M)IT/MIT is warranted as follows:

- **Acute Tox. 3, H301: Toxic if swallowed;**
- **Acute Toxicity 2, H330: Fatal if inhaled;**
- **Acute Toxicity 2, H310: Fatal in contact with skin.**

In addition, RAC is of the opinion that the additional labelling phrase **EUH071: Corrosive to the respiratory tract** is justified.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

Specific target organ toxicity following a single exposure was not considered in this dossier.

Comments received during public consultation

No comments were received regarding this endpoint.

Assessment and comparison with the classification criteria

RAC noted the available information from acute toxicity studies. Clinical signs observed during the studies following inhalation exposure of C(M)IT/MIT were consistent with respiratory irritation. These included, gasping, rales, hyperpnea, dyspnoea and exaggerated respiratory movements. Necropsy revealed congested lungs and gas-filled stomachs and/or intestines. This latter effect was deemed to be the result of swallowing of air in an attempt to breathe.

Although the data suggest that C(M)IT/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 does not propose an additional classification for STOT SE**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Several dermal studies provided relevant information to evaluate irritation/corrosion of C(M)IT/MIT by the dermal route. These studies were all performed according to OECD TG 404. The DS reported that C(M)IT/MIT was found to be corrosive to skin from a concentration of 0.75% in New-Zealand White (NZW) rabbits after 4h exposure and were found to be irreversible. No irreversible skin damage was observed in the study after a 1h exposure period. According to the DS, these results are consistent with criteria for classification with Skin Corr. 1C (H314: Causes severe burns and eye damage) with a proposed revised specific concentration limit (SCL) of C ≥ 0.5%.

Comments received during public consultation

One MS agreed with the proposed classification of Skin Corr. 1C with an SCL of C ≥ 0.5%. Another MSCA also agreed with classification for skin corrosion with an SCL of ≥ 0.5%, but questioned whether subcategorisation was appropriate because this was based on the absence of corrosivity in a 1 hour study with a low concentration. The DS responded that the proposed classification in category 1C was based on available data.

Additionally, the second MS requested adaptation of the SCL for skin irritation since the existing SCL (0.6 to 0.06%) is not in line with the proposed SCL of 0.5% for corrosion. One stakeholder organisation suggested an SCL of 0.06% ≤ C < 0.5% w/w for Skin Irrit. 2; H315 after taking into consideration the SCL of C ≥ 0.5% w/w applicable to the hazard class Skin Corr. 1C; H314.

A second industry stakeholder agreed that Skin Corr. 1C is appropriate but proposed retaining the existing SCL agreed under DSD (C ≥ 0.6%) on the basis that full reversibility of effects is observed 14-21 days after application of 0.5% dilution. This organisation also considered that the existing SCL for Skin Irrit. 2 (0.06% ≤ C < 0.6%) is adequate and should be maintained.

Another stakeholder also agreed with the proposal for categorisation of C(M)IT/MIT as Skin Corr. 1C, but since the data demonstrated that the corrosive effects of the substance were observed at 0.75% and above, the organisation proposed an SCL of 0.75% for corrosivity. Additionally, this organisation did not consider additional classification for dermal and eye irritation to be warranted. The stakeholder made reference to section 3.2.2.6 of the Guidance on the Application of the CLP Criteria, which states that substances shall be labelled as corrosive or irritating and not both.

In response to the public comments, the DS explained that the proposed lower SCL of 0.5% was retained in order to address the severity of the effects of corrosion and the available data and to update Skin Irrit. 2 (H315) with SCLs as 0.06 ≤ C < 0.5%.

As presented in Table 9 of the CLH report, a solution at 1% of the test material at 20°C has a pH of 3.4. This low pH is indicative of C(M)IT/MIT's potential to cause skin effects, which provides further support for classifying C(M)IT/MIT as corrosive.

Assessment and comparison with the classification criteria

C(M)IT/MIT currently has a harmonised classification of Skin Corr. 1B, with a specific concentration limit (SCL) of 0.6%. RAC was advised that this was translated from the classification agreed by the Commission Working Group on the Classification and Labelling of

Dangerous Substances. In addition to several animal studies, that group had also been provided with data from human case studies to show that C(M)IT/MIT (14%) is corrosive to human skin.

No human data were presented in the CLH report. However, the results of three dermal irritation studies in rabbits were presented by the DS. Two studies showed evidence of corrosivity of C(M)IT/MIT to rabbit skin whereas another seemed to show severe irritation, not skin corrosion. One of the 2 studies showing the corrosive potential of C(M)IT/MIT also provided valuable information about potency that is of relevance for the setting of a specific concentration limit for this endpoint.

In a study conducted in 1994, one NZW rabbit was exposed via the dermal route to 0.5 mL of C(M)IT/MIT (14% in water) for 4 hours. No further animals were used in this study because of the severe irreversible burn produced. Erythema was observed with a mean score value at 24, 48 and 72h of 4. There was no reversibility of erythema by day 14. Oedema, which reversed by day 7, was observed, with a mean score value of 3.7. Given the severity of the lesions observed and the irreversibility of the erythema, the test substance is considered corrosive to skin. Since the damage occurred following a 4 hour exposure, these data would support categorisation of C(M)IT/MIT in at least Skin Corr. Cat. 1C. The study did not investigate whether shorter exposure times would also produce a corrosive effect and so do not inform on the applicability of a more severe sub-categorisation.

In a study conducted in 1985, three male NZW rabbits were exposed via the dermal route to C(M)IT/MIT at concentrations of 0.25%, 0.5%, 0.75% and 1.0% for 4 hours. The mean score values at 24, 48 and 72h are presented in the table below.

Concentration	**Erythema**	**Oedema**
0.25%	2.1	2.5
Average time for reversibility	7-14 days	7-14 days
0.5%	2.5	3.3
Average time for reversibility	14-21 days	14-21 days
0.75%	3.1	3.1
Average time for reversibility	no reversibility 14 days post-treatment	no reversibility 14 days post-treatment
1.0%	3.2	3.7
Average time for reversibility	no reversibility 14 days post-treatment	no reversibility 14 days post-treatment

According to the DS, this study indicates that C(M)IT/MIT is corrosive due to the severity and irreversible damage induced by exposure to the test substance at 0.75% and 1%. At concentrations of 0.25% and 0.5%, C(M)IT/MIT produced a skin irritant effect. However, the DS did not report the observations in full, but given the existing classification of C(M)IT for corrosivity, RAC has no reason to doubt this assessment. The study did not investigate whether shorter exposure times would also produce a corrosive effect, therefore it also does not inform on the possibility of a more severe sub-categorisation than Skin Corr. 1C.

A further dermal irritation study, in which six NZW rabbits (3/group) were exposed to an aqueous solution of C(M)IT/MIT (14%) for 1 hour and 4 hours was conducted in 1986. One animal presented a well-defined erythema and a slight eschar. The mean erythema Draize score at 24, 48 and 72 hours was 2.5. A reversal of erythema was observed at 72h, with total recovery after 11 days. Oedema was severe (scored the maximum Draize score of 4) in 5 animals, whilst the other animal had moderate oedema (score = 3) one hour after patch removal. The oedema extended beyond the area of exposure. By day 3, there was evidence that the irritation had reversed (only

3 animals had a slight oedema). The mean Draize score for oedema was 2.1 (mean of 24, 48 and 72 hours) and total recovery was observed after 8 days. This study produced similar results to the 1994 study but the effects observed were not as severe and according to the CLP criteria, the results indicate severe skin irritation rather than skin corrosion. No argument was provided in the CLH report to explain why exposure to the test substance in this study elicited a less severe reaction than in the other two studies.

The data from the 1994 and 1985 studies show that C(M)IT/MIT induced severe and irreversible damage to the skin of rabbits following exposure to the substance for 4 hours. According to Section 3.2.2.6.2 of Annex I of CLP, Skin Corrosion subcategory 1C is appropriate where such responses occur after exposures between 1 hour and 4 hours and observations of up to 14 days. The basis for the current harmonised classification in sub-category 1B is unclear. No studies were conducted with shorter exposure periods, so a definitive conclusion about the applicability of a higher classification in subcategory 1A or 1B cannot be reached. However, as the effects seen in the third rabbit skin irritation study matched the criteria for classification of C(M)IT/MIT as an irritant and not a corrosive substance, a higher sub-categorisation would seem inappropriate.

Therefore, RAC agrees with the proposal to classify C(M)IT/MIT in category 1C for skin corrosion.

The existing harmonised entry for C(M)IT/MIT includes specific concentration limits of 0.6% for skin corrosion and 0.06% for skin irritation. These are considerably lower than the general limits of 5% and 1% for these hazard classes, respectively. Following comments made during the public consultation, the DS confirmed that their proposal was to reduce the limit for skin corrosion classification to 0.5% and maintain the limit for skin irritation at 0.06%. However, the CLH report does not provide an assessment of the data on the specific concentration limit previously reviewed by the Commission Working Group; in the one reliable rabbit study, a 0.5% solution of C(M)IT/MIT was only irritating to skin, not corrosive. In addition, no data have been provided to indicate that the specific concentration limit for skin irritation should be amended.

In conclusion, RAC agrees with the DS that classification as **Skin Corr. 1C** is warranted for C(M)IT/MIT. However, regarding SCLs for this hazard class, RAC proposes **no change to the existing SCL in Annex VI** of CLP:

- Skin Corr. 1C; H314: Causes severe skin burns and eye damage; C ≥ 0.6%
- Skin Irrit. 2; H315: Causes skin irritation; 0.06 ≤ C < 0.6%

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

Eye corrosion/irritation was not considered in this dossier. However, classification with skin corrosion means it is implicit that the substance will also cause serious damage to the eyes.

Comments received during public consultation

One stakeholder organisation agreed with the proposal to classify C(M)IT/MIT as Skin Corr. 1C; H314, but considered that C(M)IT/MIT does not warrant additional classification for eye irritation.

One MS requested adaptation of the proposed SCL for eye irritation. A second stakeholder organisation suggested SCLs of 0.06% ≤ C < 0.5% w/w for Eye Irrit. 2. In response, the DS

stated that their intention was to propose SCLs of 0.06 ≤ C < 0.5% w/w for Eye Irrit. 2; H319, as 0.5% is the SCL proposed for classification as corrosive to skin.

Assessment and comparison with the classification criteria

As discussed above for skin corrosion/irritation, RAC considers that the existing harmonised specific concentration limits for corrosivity and irritancy should be maintained, as the DS did not provide any clear evidence to justify changing them.

In conclusion, the existing SCLs in Annex VI of CLP are maintained for Eye Irrit. 2; H319: Causes serious eye irritation; 0.06 ≤ C < 0.6%.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS considers C(M)IT/MIT to be a potent skin sensitiser. After dermal exposure, it induced skin sensitisation effects in animals (guinea pigs and mice) and humans.

According to the results obtained in the LLNA studies in mice conducted according to OECD 429 (House, 2000a, 2000b), C(M)IT/MIT is sensitising at concentrations ≥ 30 ppm (or ≥ 0.003%) (see also the Table below).

Since 1988 the substance has been included in the European baseline patch test series and as a result, human historical data is available and summarised in the CLH report . A multicenter study within the European Environmental and Contact Dermatitis Research Group has been conducted (Bruze *et al*., 2014). Several dilutions of C(M)IT/MIT were tested to ascertain an appropriate diagnostic patch test concentration to include in a patch test series. dilution concentration of 100 ppm induced low skin irritancy and was high enough to detect most cases of sensitisation. It has been included in the European baseline patch test series since 1988. However, Sweden and some centres in Spain, in the United Kingdom and in Ireland used 200 ppm in their baseline series. Considering the results of this multicentre study, 200 ppm could be considered the optimal patch test concentration for C(M)IT/MIT since it has been demonstrated that it diagnosed significantly more contact allergy cases than a concentration of 100 ppm without inducing more adverse reactions.

Overall, the patch test data provides information establishing the optimal concentration to confirm cases of sensitisation but no new information is available to challenge the classification threshold value of 0.0015% (15 ppm) recommended by the Commission Working Group on the Classification and Labelling of Dangerous Substances in 2000 in order to avoid the induction of skin sensitisation during exposure with products containing C(M)IT/MIT.

According to the results obtained in the LLNA studies on C(M)IT/MIT, the lowest Estimated Concentration that will induce a stimulation index (SI) of 3 after topical application (EC_3 value), is 30 ppm (or 0.003%). This value is below the threshold value of 2% for classification as Skin Sens. 1A (H317: May cause an allergic skin reaction) under CLP. Overall, based on the results of the animal studies and knowledge of historical human data, the Dosser submitter proposed a classification of Skin Sens. 1A; H317. As no data were available to challenge the current specific concentration limit for this hazard class, the DS proposed that the existing SCL in Annex VI of CLP of C ≥ 0.0015%, Skin Sens. 1A (H317) should be retained.

Comments received during public consultation

Three MSCA and two industry stakeholders agreed with classification of C(M)IT/MIT as skin sensitiser Cat. 1A and retaining the specific concentration limit of 0.0015%.

One industry stakeholder reminded the DS that as a consequence of classifying C(M)IT/MIT as a skin sensitiser, the EUH208 phrase ('*Contains [name of sensitising substance]. May produce an allergic reaction*') will be required on all products containing C(M)IT/MIT above 1.5 ppm (0.00015%).

Assessment and comparison with the classification criteria

There is a large body of literature describing clinical studies and case reports in humans indicating that C(M)IT/MIT is a skin sensitiser. The data were reviewed in detail when C(M)IT/MIT was assessed by the Commission Working Group on the Classification and Labelling of Dangerous Substances during the period 1998-2000. The data contributed to the classification of C(M)IT/MIT as a skin sensitiser and to the the specific concentration limit of 0.0015%.

The following table shows the results of the animal studies presented by the DS to illustrate that C(M)IT/MIT is a potent sensitiser.

Test (date)	**Result**	**Observations and Conclusions**
LLNA (2000a) Measured doses: 0, 30, 50, 70, 90, 360, 1000ppm (0, 0.003, 0.005, 0.007, 0.009, 0.036 and 0.1% respectively)	Positive	OECD TG 429 **SI ≥ 3 for all concentrations** SI = 1.0, 3.4, 4.7, 4.2, 6.7, 20.5, 45.5 at 0, 30, 50, 70, 90, 360 and 1000 ppm respectively. **EC3 value of ≤ 2** EC3 = 0.003% Skin Sens. Cat. **1A**
LLNA (2000b) Measured doses: 0, 30, 50, 70, 90, 360, 1000ppm (0, 0.003, 0.005, 0.007, 0.009, 0.036 and 0.1% respectively)	Positive	OECD TG 429 **SI ≥ 3 from 70ppm** SI = 1.0, 1.5, 1.9, 3.4, 3.3, 6.7, 7.7 at 0, 30, 50, 70, 90, 360 and 1000 ppm respectively **EC3 value of ≤ 2** EC3 = 0.007% The data appear to show a positive result and support categorisation of C(M)IT/MIT as Skin Sens. Cat. **1A** However, the positive control did not give an SI ≥ 3, therefore the data cannot be assessed reliably.
GPMT (2000a)	Negative	OECD TG 416, GLP Very low induction concentrations used, 0.003% and 0.005% no classification

GPMT (2000b) Induction Intradermal treatment: 0.71% Dermal induction treatment: 3.55% a.i. Challenge 1.42, 1.07, 0.71, 0.355% a.i. (or 14200, 10700, 7100 and 3550 ppm a.i.) Re-challenge 0.00355, 0.000355% a.i. (or 36 and 3.6ppm a.i.)	Positive	OECD TG 416, GLP Following intradermal induction with 0.71%, the test material was applied dermally on the same site one week later. Two weeks later, the animals were challenged. The results are as follows. Challenge 3/10 control 10/10 at 1.42% a.i. (Dose group I) 10/10 at 1.07% a.i. (Dose group II) 5/10 at 0.71% a.i. (Dose group III) 3/10 at 0.355% a.i. (Dose group IV) Intense skin reactions and necrosis were observed following challenge. One week after challenge, animals in dose groups III and IV were re-challenged. Re-challenge 0/10 control 4/10 at 0.00355% a.i. (Dose group III) 0/10 at 0.000355% a.i. (Dose group IV) The result of this study appears to be positive since a positive response was observed in 40% of the test animals after re-challenge. However, it would be inappropriate to use this result to define potency given the corrosivity observed under the test conditions.
Buehler (1982)	Positive	GLP 9/15 animals responded to an induction concentration of 0.01%. Skin Sens. Cat. **1A**
Open Epicutaneous Test (2001)	Positive	Non-standard study and so sub-categorisation is not possible Skin Sens. Cat. **1**

According to Table 3.4.2 in Annex I of CLP, *substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.* Substances meeting this criteria fall into subcategory 1A. Some of the studies summarised above give potency data, which indicate that Skin Sens. 1A would be appropriate for C(M)IT/MIT.

In the CLH report, the human data have been summarised but not in sufficient detail to allow a totally independent assessment of potency. There are no data in the CLH report or in the comments received during PC to justify an alternative specific concentration limit to that already listed in the harmonised classification of C(M)IT/MIT. Significantly, no studies showing that levels < 15 ppm can lead to sensitisation have been cited. Consequently, with reference to the agreement reached previously, RAC is in agreement with the DS that there are no grounds to recommend a change to the existing specific concentration limit of 0.0015% for skin sensitisation.

As noted during the public consultation, in accordance with Annex II of the CLP Regulation, labelling phrase EUH 208 phrase (*Contains [name of sensitising substance]. May produce an allergic reaction*) will be required on all products containing C(M)IT/MIT above 1.5 ppm (0.00015%).

In conclusion, RAC agrees with the DS that C(M)IT/MIT warrants a classification as **Skin Sens. 1A; H317: May cause an allergic skin reaction**.

RAC is of the opinion that the existing SCL in Annex VI of CLP of C ≥ 0.0015% should be retained.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

The DS had originally included data about interleukins in order to present the available information on the allergenicity of C(M)IT/MIT more generally. In response to the comments received during public consultation, the DS clarified that the intention was not to make a proposal for classification for respiratory sensitisation.

Since no data have been collected specifically addressing respiratory sensitisation, the DS considered that no conclusion could be drawn on either the endpoint or the availability of data.

Comments received during public consultation

One MSCA provided a summary of a further study, see the section "Additional key elements" in the Background Document in Annex I.

One industry stakeholder considered that the scientific literature data are conclusive but not sufficient for classification.

A second industry stakeholder organisation commented that C(M)IT/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 literature.

Assessment and comparison with the classification criteria

Since there are no available data from studies specifically investigating the potential of C(M)IT/MIT to induce respiratory sensitisation, it is not possible to draw a firm conclusion on this endpoint.

RAC concludes that **no classification** is justified for this hazard class.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Reaction mass 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1); (C(M)IT/MIT) is currently listed in Annex VI to CLP (Regulation (EC) 1272/2008) as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. The DS proposed to retain the existing harmonised classification but to add separate acute and chronic M-factors of 100 to both hazard classes.
In the framework of the Biocidal Products Regulation, two applicants have provided data for the environmental section, which have been gathered and compared in the submitted CLH report.

Degradation

Summary

The available hydrolysis studies showed that MIT and C(M)IT do have moderate hydrolytic half-lives. While MIT was stable at all pHs, C(M)IT was stable at pH 5 and 7, whereas at pH 9 the half-lives were 47.8 – 120.6 days at 12°C. Regarding photodegradation in water, half-lives were 6.6 days for C(M)IT and 18.2 days for MIT. A ready biodegradation study conducted with C(M)IT/MIT following OECD TG 301D was not considered valid by the DS due to the application of adapted inoculum. However, available ready biodegradation studies (OECD TG 301B) on the constituents showed that C(M)IT and MIT are not readily biodegradable. No reliable surface water simulation test for C(M)IT/MIT was available, however, MIT and C(M)IT were tested separately in marine and estuarine water (OECD TG 309). The worst case primary degradation DT_{50}s of C(M)IT and MIT in marine water at 9 °C were 41.7 and 29.7 days, respectively. In addition, simulation studies in estuarine water and in water/sediment (OECD TG 308) are available on C(M)IT and MIT showing that primary degradation half-lives were < 16 days, however, not all relevant metabolites were identified. Further details on the available degradation studies can be found in the background document to the opinion (Annex 1).

Taking into consideration the available information the DS conluded that based on a weight of evidence approach, C(M)IT/MIT cannot be considered as rapidly degradable for classification purposes.

Bioaccumulation

In the CLH report experimental log Kow values (determined at 24 °C) of 0.63 to 0.71 for C(M)IT and of -0.48 to -0.26 for MIT are reported, indicating no potential for bioaccumulation.

The DS furthermore reported a BCF value of 3.162, estimated by QSAR for C(M)IT, MIT and metabolites, and an experimental BCF value for MIT (2.32) and for C(M)IT (in the range 11-51) was reported without further reference to the studies.

Aquatic toxicity

Four acute and two chronic aquatic toxicity tests to freshwater fish are available; two other acute tests to saltwater fish are also available. All tests were carried out with C(M)IT/MIT 14% and standard guidelines were followed.

Two acute and two chronic aquatic toxicity tests to freshwater invertebrates are available, four other acute tests to saltwater invertebrates are also available. All tests were carried out with C(M)IT/MIT 14%, and standard guidelines were followed.

Three toxicity tests, two on freshwater algae and one on marine water diatom are available from studies with C(M)IT/MIT, following standard guidelines.

In the following table a summary of the relevant information on aquatic toxicity studies is reported.

Table: Summary of relevant information on aquatic toxicity.

Method	Test organism	Conditions	Endpoint	Toxicity values in mg a.s./L	Reference
Short-term toxicity to fish					
US EPA FIFRA 72-1 Freshwater	*Oncorhynchus mykiss*	Flow-through mm	96-h LC_{50}	0.19	Ward and Boeri, 1990a/ Dow
US EPA FIFRA 72-1 Freshwater	*Lepomis macrochirus*	Flow-through mm	96-h LC_{50}	0.28	Ward and Boeri, 1990b/ Dow
OECD TG 203 Freshwater	*Oncorhynchus mykiss*	Static nom	96-h LC_{50}	0.22	Wyness, 1994a/ Thor
OECD TG 204 Freshwater	*Oncorhynchus mykiss*	Flow-through mm	14-d LC_{50}	0.09	Ward and Boeri, 1991a/ Dow
American Society for Testing Materials Committee E-35 on Pesticides, 1980 Marine water	*Cyprinodon variegatus*	Static nom	96-h LC_{50}	0.30	Heitmuller *et al*., 1980/ Dow
US EPA FIFRA 72-4 Marine water	*Cyprinodon variegatus*	Flow-through nom	96-h LC_{50}	0.48	Boeri, 1998/ Thor
Long-term toxicity to fish					
US EPA FIFRA 72-4 Freshwater	*Pimephales promelas*	Flow-through mm	36-d NOEC (based on weight) 36-d NOEC (based on percent survival at hatch, mortality of embryos, mortality of larvae and juveniles and total length)	0.02 0.12	Ward and Boeri, 1991b/ Dow
OECD TG 215 Freshwater	*Oncorhynchus mykiss*	Semi-Static nom	28-d NOEC (based on weight)	0.098	Scheerbaum, 1999/ Thor
Short-term toxicity to aquatic invertebrates					
US EPA 72-2 Freshwater	*Daphnia magna*	Flow-through mm	48-h EC_{50}	0.16	Ward and Boeri, 1990c/ Dow
OECD TG 202 Freshwater	*Daphnia magna*	Static nom	48-h EC_{50}	0.10[a]	Mattock, 1996/ Thor

Method	Test organism	Conditions	Endpoint	Toxicity values in mg a.s./L	Reference
Short-term toxicity to fish					
US EPA OPPTS 850.1035 Saltwater	*Americamysis bahia*	Flow-through mm	96-h LC_{50}	0.282	Palmer *et al.*, 2002/ Dow
USEPA 72-3 Saltwater	*Mysidopsis bahia*	Flow-through nom	96-h LC_{50}	0.33	Boeri, 1998b/ Thor
ISO TC 147/SC 5/WG 2: and PARCOM Ring Test Protocol Saltwater	*Acartia tonsa*	Static nom	96-h LC_{50}	0.007	Weideborg, 1995/ Dow
EPA 72-3 (b)850.1350 Saltwater	*Crassostrea virginica*	Flow-through nom	96-h EC_{50}	0.041 (based on shell deposition)	Boeri *et al.*, 1998/ Thor
Long-term toxicity to aquatic invertebrates					
US EPA 72-4	*Daphnia magna*	Flow-through mm	21-d NOEC	0.10	Ward and Boeri, 1991c/ Dow
OECD TG 202 Part II	*Daphnia magna*	Semi-Static mm	21-d NOEC	0.0036[a]	Mattock, 1996/ Thor
Toxicity to algae					
OECD TG 201 ISO 8692 US EPA FIFRA 122-2 Freshwater	*Pseudokirchneriella subcapitata (Selenastrum capricornutum)*	24h Static imc (LOQ/2)	NOE_rC	$4.995\ 10^{-3}$	Boeri *et al.*, 1995a/ Dow RI: 2
OECD TG 201 US EPA OPPTS 850.5400 Freshwater	*Pseudokirchneriella subcapitata*	72h Static mm	E_rC_{50} NOE_rC	$53.5\ 10^{-3}$ $0.49\ 10^{-3}$	Scheerbaum, 2008/ Thor RI: 1
OECD TG 201 US EPA OPPTS 850.5400 Saltwater	***Skeletonema costatum***	48h Static mm	**E_rC_{50}** **NOE_rC**	**$5.2\ 10^{-3}$** **$0.49\ 10^{-3}$**	Palmer *et al.*, 2009/ Dow RI: 1

mm – mean measured concentration
imc – initial measured concentration
nom – nominal concentration
a) test was carried out with C(M)IT/ MIT 2.1% instead of 14% in all others ecotoxicity tests
Key endpoints used in acute and long-term hazard classification are highlighted in bold.

All toxicity tests indicate that the substance is very toxic to fish. Almost all toxicity tests with invertebrates, both freshwater and saltwater, indicate that C(M)IT/MIT is also very toxic to this trophic level.

Algae is the most sensitive taxonomic group for this substance. Due to the peculiar mode of action of C(M)IT/MIT, linked to the algal concentration, initial cells density of each study has been carefully checked and endpoints have been daily assessed to determine the most sensitive period. Depending of the relevant period, endpoints are expressed as initial measured concentrations or as geometric mean of measured concentrations.

The key study on the aquatic algae *Skeletonema costatum* showed a rapid decline of the active substance concentration, due to its mode of action. The degradation of C(M)IT/MIT depends on algal concentration, because the substance determines an inhibitory effect on the enzymes of the algae, which will result in degradation of C(M)IT/MIT. At higher test concentrations, growth of algae is inhibited which in turn slows down the degradation of the substance by algae. In order to correctly assess the concentration of the substance in the test media, analytical measurements were performed every 24h. Since statistics indicate that the period of major sensibility of the algae relay within the first two days, the endpoints were determined as mean measured concentrations at 48h.

Moreover, three major metabolites of C(M)IT/MIT were identified: NMMA, NMA and MA. Acute toxicity data of these metabolites are available for all three trophic levels (Table below).

Table: Summary of relevant information on aquatic toxicity of C(M)IT/MIT metabolites (NMMA, NMA and MA).

Method	Test organism	Conditions/Metabolite	Endpoint	Toxicity values in mg a.s./L	Reference
Short-term toxicity to fish					
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static nom N-methyl malonamic acid (NMMA)	96-h LC_{50}	>1000	Madsen, 2002a/ Dow
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static mm N-methyl acetamide (NMA)	96-h LC_{50}	>694	Rhodes, 2002a/ Dow
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static nom malonamic acid (MA)	96-h LC_{50}	>1000	Madsen, 2002b/ Dow
Short-term toxicity to aquatic invertebrates					
OECD TG 202, US EPA OPPTS 850.1010, US EPA 797.1300, US EPA 72-2 Freshwater	*Daphnia magna*	Static mm N-methyl acetamide (NMA)	48-h EC_{50}	>>863	Madsen, 2002c/ Dow

Method	Test organism	Conditions/Metabolite	Endpoint	Toxicity values in mg a.s./L	Reference
Short-term toxicity to fish					
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static nom N-methyl malonamic acid (NMMA)	96-h LC_{50}	>1000	Madsen, 2002a/ Dow
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static mm N-methyl acetamide (NMA)	96-h LC_{50}	>694	Rhodes, 2002a/ Dow
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static nom malonamic acid (MA)	96-h LC_{50}	>1000	Madsen, 2002b/ Dow
Short-term toxicity to aquatic invertebrates					
OECD TG 202, US EPA OPPTS 850.1010, US EPA 797.1300, US EPA 72-2 Freshwater	*Daphnia magna*	Static mm N-methyl malonamic acid (NMMA)	48-h EC_{50}	>>986	Rhodes, 2002b/ Dow
OECD TG 202, US EPA OPPTS 850.1010, US EPA 797.1300, US EPA 72-2 Freshwater	*Daphnia magna*	Static nom malonamic acid (MA)	48-h EC_{50}	> 1000	Madsen, 2002d/ Dow
Toxicity to algae					
OECD TG 201 US EPA OPPTS 850.5400	*Pseudokirchneriella subcapitata*	96h-Static imc N-methyl malonamic acid (NMMA)	96-h E_rC_{50} 96-h NOE_rC	128 36	Madsen, 2002e/ Dow RI:1
OECD TG 201 US EPA OPPTS 850.5400	*Pseudokirchneriella subcapitata*	72h-Static imc N-methyil acetamide (NMA)	72-h E_rC_{50} 72-h NOE_rC	5.8 0.51	Rhodes, 2002c/ Dow RI:2

Method	Test organism	Conditions/Metabolite	Endpoint	Toxicity values in mg a.s./L	Reference
Short-term toxicity to fish					
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static nom N-methyl malonamic acid (NMMA)	96-h LC_{50}	>1000	Madsen, 2002a/ Dow
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static mm N-methyl acetamide (NMA)	96-h LC_{50}	>694	Rhodes, 2002a/ Dow
OECD TG 203, US EPA OPPTS 850.1075, US EPA 797.1400, US EPA 72-1, and EC Council Directive 91/414/EC Freshwater	*Oncorhynchus mykiss*	Static nom malonamic acid (MA)	96-h LC_{50}	>1000	Madsen, 2002b/ Dow
Short-term toxicity to aquatic invertebrates					
OECD TG 201 US EPA OPPTS 850.5400 US EPA TSCA 797.1050 US EPA FIFRA 122-2 and 123-2 EC Council Directive 67/548/EEC	*Pseudokirchneriella subcapitata*	96h-Static imc Malonamic acid (MA)	96-h E_rC_{50} 96-h NOE_rC	> 1080 519	Madsen, 2002f/ Dow RI:1
mm – mean measured concentration nom – nominal concentration imc – initial measured concentration					

Short-term toxicity tests to fish and aquatic invertebrates indicate that all three metabolites are practically non-toxic for these trophic level. All three metabolites are less toxic to freshwater algae than the parent C(M)IT/MIT. However, an algae NOEC value of 0.51 mg/L for NMA shows that this metabolite is toxic to algae.

Comments received during the public consultation

Two MSCAs and three companies commented on the proposed environmental classification.

For one MSCA it was not clear if the validity criteria of the exponential growth in controls of the key algae study was fulfilled and if a minimum multiplication factor of 16 was reached after 48h of the test period. The DS stated in his response to comments that the above conditions were met.

All three commenting companies disagreed with the proposed environmental classification, particularly with the M-factor of 100 for the long-term aquatic hazard classification. They considered CMIT/MIT and their metabolites being rapidly degradable. The DS confirmed that for several simulation degradation studies, the DT_{50}s for primary degradation were below 16 days and the metabolites have been shown to be readily biodegradable. Nevertheless, in marine water, a DT_{50} for primary degradation of >16 days was observed for the highest tested concentration (100 µg/L) and C(M)IT/MIT cannot therefore be considered rapidly degradable. Moreover, MIT was considered 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 fulfil the criteria for classification as hazardous to the aquatic environment.

One company proposed to use the 24h measured CMIT/MIT concentrations to derive the toxicity endpoints based on the specific mode of action of CMIT/MIT in bacteria, fungi and algal cells and its rapid time course and disagreed with the use of the 48h toxicity endpoints. The DS agreed with the analysis of the effects on algae but highlighted that the validity criteria mentioned in the comment were not clear. In addition, the DS questioned whether endpoints at 24h can be considered as chronic endpoints.

Another company expressed doubts about the long-term hazard classification based on the algal endpoint because of the substance rapid dissipation from the test media. Moreover, the company did not consider it feasible to use shortened exposure times in algae tests and proposed a weight of evidence approach using another ecotoxicity study on the marine copepod *Acartia tonsa* (Weideborg, 1995). The DS noted that since the validity criteria were fulfilled at 48h in the algal study, there is no need to provide more information on the validity of the study carried out with *A. tonsa*.

The last company did not agree on a classification based on 48h E_rC_{50}/NOE_rC values. Following that consideration, it was proposed to classify C(M)IT/MIT using 72h E_rC_{50} value, which will lead to an acute M-factor of 10. The DS replied that in the study with the marine algae a multiplication factor of 55 was reported after 48h for cell density in the controls which supported study conditions generating exponential growth. The endpoints derived at 48h were therefore considered relevant for the acute and long-term hazard classifications.

Assessment and comparison with the classification criteria

Degradation

Regarding hydrolysis, MIT is stable at all pH, C(M)IT was stable at pH 5 and 7 while at pH 9 the half-lives were 47.8 – 120.6 days at 12°C.

Regarding photodegradation in water, half-lives were 6.6 days for C(M)IT and 18.2 days for MIT.

In a ready biodegradation study on C(M)IT/MIT the threshold was reached. Nevertheless, as the test was carried out with an activated sludge receiving both domestic wastewater and chemical

waste, adaptation of the inoculum cannot be excluded and C(M)IT/MIT this study was therefore considered not valid for classification purposes. The ready biodegradation studies on the constituents of the substance show that C(M)IT and MIT are not readily biodegradable.

No reliable surface water simulation tests for C(M)IT/MIT are available. However, simulation studies in marine and estuarine water were performed on each of the constituents separately. The worst case primary degradation DT_{50}s of C(M)IT and MIT in marine water at 9°C are 41.7 and 29.7 days, respectively, therefore the single constituents of the substance were demonstrated to be not primarily degraded with half-lives of < 16 days. Furthermore, even if the primary degradation half-lives in the estuarine water studies and in the water sediment studies on the constituents were < 16 days, some relevant metabolites were not identified. In addition, the transformation product NMA is considered classifiable as Aquatic Chronic 3, based on an algae NOEC value of 0.51 mg/L and rapid degradability. In light of this information, C(M)IT and MIT are separately considered as not rapidly degradable.

Based on the above weight of evidence, C(M)IT/MIT is considered not to be rapidly degradable for classification purposes.

Bioaccumulation

The experimental log Kow at 24 °C of MIT is -0.486 and log Kow of C(M)IT is 0.401, these values are more than four orders of magnitude lower than the trigger value (> 4) in the CLP Regulation.

Aquatic toxicity

Acute aquatic toxicity data are available for all three trophic levels. The most acutely sensitive trophic group is algae with a 48h E_rC_{50} value for *Skeletonema costatum* of 0.0052 mg/L. This acute endpoint is in the range of $0.001 < L(E)C_{50} \leq 0.01$ mg/L.

Chronic aquatic toxicity data are available for all three trophic levels. The most acutely sensitive trophic group is algae with a 48h NOE_rC value for *Skeletonema costatum* of 0.00049 mg/L. This chronic endpoint is in the range of $0.0001 < NOEC \leq 0.001$ mg/L.

Conclusion on the classification

C(M)IT/MIT is considered not rapidly degradable and does not fulfil the criteria for bioaccumulation potential. The lowest acute aquatic toxicity value falls in the range $0.001 < L(E)C_{50} \leq 0.01$ mg/L and the lowest chronic aquatic toxicity value lies in the toxicity range of $0.0001 < NOEC \leq 0.001$ mg/L.

RAC concluded that C(M)IT/MIT fulfils the CLP criteria for classification as **Aquatic Acute 1; H400** with an **M-factor of 100** and **Aquatic Chronic 1; H410** with an **M-factor of 100.**

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and by RAC (excluding confidential information).