Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report

C(M)IT/MIT

Product-type 13

(Biocide for use as working or cutting fluid preservatives)

June 2015

France

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1 STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 PRINCIPLE OF EVALUATION AND PROCEDURE FOLLOWED

This Competent Authority report has been established as a result of the evaluation of the active substance C(M)IT/MIT: 5-chloro-2-methylisothiazol-3(2H)-one (C(M)IT) and 2-methylisothiazol-3(2H)-one (MIT) in ratio (3:1), with CAS Nr. 26172-55-4 for C(M)IT, 2682-20-4 for MIT and 55965-84-9 for the mixture, as product-type 13 (working or cutting fluid preservatives), carried out in the context of the work program for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with the original view to the possible inclusion of this substance into Annex I or IA to that Directive, then carried out in the context of Regulation (EU) No 528/2012[2], with a view to the possible approval of this active substance

The evaluation has therefore been conducted to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product-type 13 containing C(M)IT/MIT that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that Directive.

C(M)IT/MIT was notified as an existing active substance, by Rohm and Haas Europe Trading ApS, now a subsidiary of The Dow Chemical Company (hereafter referenced as "Dow")" and Thor in product-type 13.

Data submitted were collected to compile a single dossier on the hazard assessment of the active substance. Therefore, there will be references to the data submitted by both manufacturers Dow and Thor in this report.

Commission Regulation (EC) N° 1451/2007 of the 4th of December 2007[3] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into the Annex I or IA of the Directive.

In accordance with the provisions of Article 3 paragraph 2 of that Regulation, France was designated as Reporter Member State to carry out the assessment of C(M)IT/MIT on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for C(M)IT/MIT as an active substance in product-type 13 was the 31st of July 2007, in accordance with Article 9 paragraph 2 of Regulation (EC) N° 1451/2007.

On the 15th of June 2007 and on the 31st of July 2007, the French competent authority received a dossier from Dow and Thor. The Rapporter Member State accepted the dossier as complete for the purpose of the evaluation, taking into account the supported uses, and confirmed the acceptance of this dossier on the 5th of February 2008.
On 27th of November 2012, the Rapporteur Member State submitted to the Commission, the applicant and the others members states a copy of the evaluation report, hereafter referred to as the competent authority report (CAR).

[1] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market, OJ L 123, 24.4.98, p.1
[2] Regulation (EU n° 528/2012 of the European Parliament and of the council o 22 May 2012 concerning the making available on the market and use of biocidal products.
[3] Regulation EC n° 1451/2007 of december 2007 on the second phase of 10-year work programme referred to in article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing biocidal products on the market OJ L 325, 11.12.2007, p. 3.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2 PURPOSE OF THE ASSESSMENT

The aim of the Competent Authority report is to support a decision on the approval of C(M)IT/MIT for product-type 13, and should it be approved, to facilitate the authorisation of individual biocidal products in product-type 13 that contain C(M)IT/MIT. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

2 OVERALL SUMMARY AND CONCLUSIONS

2.1 PRESENTATION OF THE ACTIVE SUBSTANCE

2.1.1 Identity, Physico-Chemical properties & Methods of Analysis

2.1.1.1 Active substance

The active substance as manufactured is a mixture of 5-chloro-2-methylisothiazol-3(2H)-one (C(M)IT) and 2-methylisothiazol-3(2H)-one (MIT)[4] in ratio (3:1), with CAS Nr. 26172-55-4 for C(M)IT and 2682-20-4 for MIT and 55965-84-9 for the mixture. The active ingredient is named C(M)IT/MIT (3:1).

The active substance is manufactured as a technical concentrate (TK) with different solvents and stabilizers. The minimum purity of the technical material (TC) has been theoretically calculated based on the composition of the solutions. The different solutions have been assessed and four are acceptable and proposed as reference source with a minimum purity for the TC of: 57.9% of C(M)IT/MIT 3:1 in dry weight.
Among the different stabilisers used, two are of concern: magnesium nitrate and magnesium chloride.
Please see the confidential annex: Confidential appendix to doc IIA for details of accepted sources and calculation.

The notified active substance is manufactured by two different applicants: Thor and Dow.

C(M)IT/MIT (3:1) is very reactive with some substances and should be stabilized in the product. That is the reason why the active substance is manufactured in continuous directly at the product stage. The product mostly on the market is a solution 14% in water with stabilizers salts and most of the (eco)toxicological studies have been performed with this solution. There are three sources for this solution.
C(M)IT/MIT (3:1) at 14% in water with stabilizers is a clear liquid, colourless to pale yellow with a mild odour. It is not flammable and does not have explosive and oxidising properties. As it is classified as a corrosive substance, aluminium, grey cast iron and steel (except some approved high-grade steels) are not suitable materials. There is no reactivity with high density PE containers, glass, PP, PVC, glass fibre reinforced plastics.

C(M)IT/MIT (3:1) has a low volatility and vapour pressure at 20°C. C(M)IT and MIT are extremely soluble in water and are not bioaccumulable (log K_{ow} are respectively 0.401 for C(M)IT and -0.486 for MIT).

Validated methods for analysis of C(M)IT, MIT, additives and impurities in the active substance as manufactured have been provided. However for one additive and for the impurities for Thor, validation data are required to validate the analytical method used in the 5-batch analysis. Moreover some validation data are missing to fully validate the analytical methods used in the 5-batch analysis: complete validation data for one impurity in one source and for another impurity in another source for Dow.

Validated methods for analysis of residues of C(M)IT and MIT in soil and sediments, air, drinking and surface water and simulated food have been provided. A confirmation method for the determination of C(M)IT/MIT in soil is missing however due to the rapid degradation of C(M)IT and MIT in soil, the confirmatory method is not required. Thor has

[4] Mixture of 5-chloro-2-methylisothiazol-3(2H)-one and 2-methylisothiazol-3(2H)-one : CAS Name
Reaction mass of 5-chloro-2-methylisothiazol-3(2H)-one and 2-methylisothiazol-3(2H)-one: REACH name

not submitted methods for analysis of C(M)IT and MIT in soil and sediments and in food. It has been accepted for food as no exposure is expected for this compartment and for soil due to the rapid degradation of C(M)IT and MIT in soil..

It has been accepted that no method for determination of residues of C(M)IT and MIT in animals and human body fluids and tissues was provided, according to toxicological consideration.

The active substance hereafter named C(M)IT/MIT refers to the solution of C(M)IT/MIT (3:1) at 14% in water. In the full CAR, it is also referred to the active ingredient C(M)IT/MIT or C(M)IT/MIT at 100%, meaning to C(M)IT/MIT (3:1) without water and additives.

2.1.1.2 Biocidal products

2.1.1.2.1 Dow Chemical's product: KathonTM 886F

Dow's product contains between 12.21 and 15.78 % w/w of C(M)IT/MIT (3:1) in water.

KathonTM 886F is a clear liquid, colourless to pale yellow with a mild odour. It is not flammable and does not have explosive and oxidising properties.

Validated methods for analysis of C(M)IT and MIT in the formulation are the same as analytical methods for the determination of C(M)IT and MIT in the technical active substance.

2.1.1.2.2 Thor GmbH's product: Acticide® 14

Thor's product is Acticide® 14 which contains between 13.9 and 14.4% w/w of C(M)IT/MIT (3:1) in water.

Acticide® 14 is a clear liquid, colourless to pale yellow with a mild odour. It is not flammable and does not have explosive and oxidising properties. It is thermally stable at low (0°C) and ambient temperatures. Acidity according to CIPAC method MT31 and information about compatibility of Acticide® 14 with other products which will be used with are lacking and will have to be submitted at the product authorisation stage.

Validated methods for analysis of C(M)IT and MIT in the formulation are the same as analytical methods for the determination of C(M)IT and MIT in the technical active substance.

2.1.2 Intended uses and efficacy

2.1.2.1 Field of use / Function / Mode of action

2.1.2.1.1 Field of use

C(M)IT/MIT is intended to be used as a working or cutting fluid preservatives (product type 13).

2.1.2.1.2 Function

C(M)IT/MIT is an antimicrobial agent used for preventing the growth of microorganisms (bacteria and fungi) that may occur in metalworking fluids. C(M)IT/MIT exhibits rapid inhibition of growth at low levels and cidal effects at higher levels and for longer contact periods.

2.1.2.1.3 Mode of action

The mode of action of C(M)IT/MIT has been studied and it has been shown that C(M)IT/MIT utilizes a two-step mechanism of action involving rapid binding to cells and inhibition of growth and metabolism (within minutes), followed by irreversible cell damage resulting in loss of viability (within hours). Growth inhibition is the result of rapid disruption of the central metabolic pathways of the cell by inhibition of several specific (thiol-containing) dehydrogenase enzymes involved in the tricarboxylic acid (Krebs) cycle and electron transport (NADH). 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 produced within the cells which also results in cell death.

2.1.2.2 Objects to be protected, Target organisms

C(M)IT/MIT was shown to be an effective antimicrobial agent when tested in standard biocide efficacy tests. Minimum Inhibitory Concentration (MIC) studies were conducted to demonstrate the lowest level of biocide which inhibits the growth of common spoilage microorganisms (bacteria and fungi). Additional studies performed by Dow showed cidal effects of C(MI)T/MIT against mixed pools of bacteria and fungi. The organisms and rates for which efficacy of C(M)IT/MIT has been proved sufficiency are presented in the table below.
List of intended uses and application rates are presented in Appendix II.

Organism and rates for which efficacy of the active substance, C(M)IT/MIT, has been proved sufficiency:

Application mode	Effect	Target organism	a.i. rate	Applicant
Dilution in the metalworking fluids	Static et cide	Bacteria and Fungi	10 to 35 ppm ai	Dow
Dilution in the metalworking fluids	Static et cide	Bacteria and Fungi	14 to 42 ppm ai	Thor

2.1.2.3 Resistance

The organisms with most frequently reported resistance to C(M)IT/MIT are Gram negative bacteria, such as *Pseudomonas* and *Burkholderia*. Resistance to increasing levels of C(M)IT/MIT was shown for bacteria adapted in lab cultures. Under-dosing or poor stability of C(M)IT/MIT was attributed as the primary cause of developing the resistant strains in metalworking fluid systems, which displayed stronger resistance than the lab-adapted

isolates. The mechanism of resistance to C(M)IT/MIT biocide has been suggested to involve the loss of specific outer membrane (porin) proteins (35-42 k Dalton mass) resulting in reduced transport of C(M)IT/MIT to the interior of the cell. The vast majority of resistance attributed to C(M)IT/MIT is the result of phenotypic changes (adaptation) and does not represent a change in resistance due to altered genetic composition or mutation (acquired resistance). Microorganisms deemed resistance to C(M)IT/MIT have also shown varying degrees of cross-resistance to other Biocides. In commercial use, C(M)IT/MIT is often used in combination or rotation with other biocides in various applications. Microbial resistance to C(M)IT/MIT could be remedied by switching or alternating biocides, using combinations with other actives.

2.1.3 Classification and Labelling

2.1.3.1 Current classification

- Active substance

Directive 67/548/EEC	
Class of danger	T - Toxic C - Corrosive N - Dangerous for the environment
R phrases	R23/24/25: Toxic by inhalation, in contact with skin and if swallowed. R34: Causes burns. R43: May cause sensitization by skin contact. R50-53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
S phrases	S2: Keep out of the reach of children. S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S28: After contact with skin, wash immediately with plenty of water S36/37/39: Wear suitable protective clothing, gloves and eye/face protection. S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). S60: This material and its container must be disposed of as hazardous waste. S61: Avoid release to the environment. Refer to special instructions/Safety data sheets.
Specific concentration limit	C, R34: Causes burns C ≥ 0.6% Xi, R36/38: Irritating to eyes and skin 0.06% ≤ C < 0.6% Xi; R43: May cause sensitization by skin contact C ≥ 0.0015%
Regulation 1272/2008	
Hazard classes and categories / hazard statements	Acute Tox. 3/H331: Toxic if inhaled Acute Tox. 3/H311: Toxic in contact with skin Acute Tox. 3/H301: Toxic if swallowed Skin Corr. 1B/H314: Causes severe skin burns and eye damage Skin Sens. 1/H317: May cause an allergic skin reaction Aquatic Acute 1/H400: Very toxic to aquatic life Aquatic chronic/H410 Very toxic to aquatic life with long

	lasting effects.
Specific concentration limit	Skin Corr. 1B; H314: Causes severe skin burns and eye damage C ≥ 0.6% Eye Irrit. 2; H319: Causes serious eye irritation Skin Irrit. 2; H315: Causes skin irritation 0.06% ≤ C < 0.6% Skin Sens.1/H317: May cause an allergic skin reaction C ≥ 0.0015%

2.1.3.2 Proposed classification

- Active substance

Directive 67/548/EEC		
	C(M)IT/MIT 14%	C(M)IT/MIT 3:1 100%
Class of danger	Xn: Harmful C: Corrosive Xi: Irritant N: Dangerous to the environment	T+: Very toxic C: Corrosive Xi: Irritant N: Dangerous for the environment
R phrases	R20/21/22: Harmful by inhalation, in contact with skin and if swallowed R34: Causes burns. (R37 : Irritating to the respiratory tract) R43: May cause sensitization by skin contact R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.	R26/24/25*: Very toxic by inhalation, toxic in contact with skin and if swallowed. R34: Causes burns. (R37 : Irritating to the respiratory tract) R43: May cause sensitization by skin contact. R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
S phrases	S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S28: After contact with skin, wash immediately with plenty of water S36/37/39: Wear suitable protective clothing, gloves and eye/face protection. S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). S60: This material and its container must be disposed of as hazardous waste. S61: Avoid release to the environment. Refer to special instructions/Safety data sheets.	
Specific concentration limit	C, R34: Causes burns C ≥ 0.6% Xi, R36/38: Irritating to eyes and skin 0.06% ≤ C < 0.6% Xi; R43: May cause sensitization by skin contact C ≥ 0.0015% This specific concentration limit is considered as relevant for this dossier.	
Regulation 1272/2008		

Hazard classes and categories	Acute Tox 4 for acute oral hazard Acute Tox 3 for acute dermal hazard Acute Tox 4 for inhalation hazard Skin Corr. 1B** Skin Sens. 1A STOT SE 3 Aquatic Acute 1 Aquatic Chronic 1	Acute Tox. 3 for acute oral hazard Acute Tox 2 for acute dermal hazard Acute Tox 2 for acute inhalation hazard Skin Corr. 1B** Skin Sens. 1A STOT SE 3 Aquatic Acute 1 Aquatic Chronic 1
Hazard statements	H332: Harmful if inhaled H312: Harmful in contact with skin H302: Harmful if swallowed H 314: Causes severe skin burns and eye damage** H 317: May cause an allergic skin reaction (H 335: May cause respiratory irritation) H400: Very toxic to aquatic life M-factor=10 H410: Very toxic to aquatic life with long lasting effects M-factor=10	H 330: Fatal if inhaled H 310: fatal in contact with skin H 301: Toxic if swallowed H 314: Causes severe skin burns and eye damage** H 317: May cause an allergic skin reaction (H 335: May cause respiratory irritation) H400: Very toxic to aquatic life M-factor=100 H410: Very toxic to aquatic life with long lasting effects M-factor=100
Specific concentration limit	Skin Corr. 1B; H314: Causes severe skin burns and eye damage C ≥ 0.6%** Eye Irrit. 2; H319: Causes serious eye irritation Skin Irrit. 2; H315: Causes skin irritation 0.06% ≤ C < 0.6% Skin Sens.Cat 1A/H317: May cause an allergic skin reaction C ≥ 0.0015% This specific concentration limit is considered relevant for this dossier.	

* The C(M)IT/MIT has been supported by two different applicants. There is a disputation concerning the classification for the acute respiratory exposure, since different studies have been provided by the two applicants. This point will probably lead to an Annex XV dossier for a harmonised classification for C(M)IT/MIT. Additionally, although not readily biodegradable, C(M)IT/MIT has been shown to be fast degraded in several environmental compartment and it should be stated by ECHA is it can be considered as rapidly biodegradable in the frame of the Regulation 1272/2008. At present, contradictory results are available and C(M)IT/MIT is considered as not rapidly biodegradable by the RMS, based on a weight of evidence approach. More explanations are provided in the document IIA and IIIA9. A final decision should be made by ECHA.

** A classification as Skin Corr. 1C H 314: Causes severe skin burns and eye damage should be required due to the study results, however a harmonised classification as Skin Corr. 1B has been set, and therefore this classification is retained in the dossier.

2.2 SUMMARY OF THE RISK ASSESSMENT

2.2.1 Human health Risk Assessment

2.2.1.1 Hazard identification

C(M)IT/MIT induces a local irritation observed by oral, dermal and inhalation routes. No real systemic effects were observed in any available study, except on body weight gain and food consumption. These effects are considered as secondary to the local toxicity.

2.2.1.2 Effects assessment

Toxicokinetics

- Absorption

Absorption studies were conducted in rats, following administration of C(M)IT/MIT with either ^{14}C-CMIT or ^{14}C-MIT. Bile-duct cannulation was not systematically performed.
From this overall data set, it seems that MIT would be better absorbed than C(M)IT (55-90% versus 37-62%respectively). It is generally preferred to use data from studies where animals were cannulated, the study showed the absorption rates of 49% and 78% for C(M)IT and MIT respectively (Dow A6.2c/01).It is therefore proposed to choose the lowest absorption rate value of 49%, rounded to 50% as a worst case.

The overall oral absorption rate to be used for a systemic risk characterisation is therefore 50%.

Dermal absorption was investigated in both *in vitro* (in rat and human skin) and *in vivo* (in rats).
Based on all these data, and also due to uncertainties in some studies (poor recovery, poor description of the study), it is proposed to set the dermal absorption of C(M)IT/MIT 3:1 at **50 % for aqueous solutions below corrosive concentrations**. This value is based on the maximal absorption found in an *in vitro* study 43% rounded to 50 % due to uncertainties.
Moreover, this value is in line with the EFSA guidance document for dermal absorption as a value of 50 % for oral absorption as been set.
For **corrosive concentrations** of C(M)IT/MIT (> 0.6% the specific concentration limit), no study is available, but as for the other substances of the same family it can be assumed that a **100 %** dermal absorption is appropriate.
A default inhalation absorption value of 100% has been adopted.

- Distribution

Rat tissues contain up to 4.72% of dosed radioactivity, four days after exposure. The highest amount of radioactivity is found in blood, particularly in red blood cells (up to 4.11%), followed by muscle and liver. Therefore, C(M)IT/MIT is not considered to have an accumulative potential in human.

- Metabolism

Following an oral administration of C(M)IT in solution with MIT, approximately twenty-nine radioactive components were observed in urine and faeces samples of rats from the HPLC radioprofiling. No parent compound was detected in excreta, indicating an extensive metabolization of CMIT. The major component in urine was N-methyl malonamic acid,

NMMA (M1A) (15.35-18.19%), and the major component in the faeces was the 3-mercapturic acid conjugate of 3-sulfinyl-N-methyl-propionamide (M15) (up to 32.54%) (it was found as a minor metabolite in urine). In bile-duct cannulated rats, M15 accounted for 8.83% of the dose in faeces, and was not detected in urine, indicating either that M15 may have been formed in the intestine and the cannulation has possibly broken up the entero-hepatic circulation, or the M15 may have been mainly produced at the hepatic level and is then excreted in the bile. All of the ten metabolites found in bile accounted for less than 5% of the dose.

- Excretion

MIT and C(M)IT are both rapidly excreted. Urine and faeces are equal major routes of excretion for CMIT whereas bile is a minor route of excretion (4.74%). On the contrary, MIT is largely excreted in urine and in a lesser extent in faeces, of which the major part came from the bile (29.09%).

No parent compound is present in excreta.

Acute toxicity

The acute oral LD_{50} of C(M)IT/MIT in rats ranges from 457 to 472 mg/kg bw (corr. to 64 to 66 mg a.i./kg bw). Dead animals show effects on stomach and intestines which are consistent with the corrosive properties of C(M)IT/MIT. Therefore, C(M)IT/MIT meets the EU criteria for classification as 'Harmful if swallowed' and should be classified as Xn; R22 (corr. to 'toxic if swallowed', T; R25 for C(M)IT/MIT 3:1) according to the directive 67/548/EC. A classification as Acute Tox 4 / H302: Harmful if swallowed is required according to the regulation 1272/2008/EC (corr. to Acute Tox. 3 /H 301: Toxic if swallowed for C(M)IT/MIT 100 %).

The acute dermal LD_{50} of C(M)IT/MIT in male rabbits is 660 mg/kg bw (corr. to 87 mg a.i/kg bw). In rats, the acute dermal LD_{50} is 1008 mg/kg bw (corr. to 141 mg a.i/kg bw). Observed effects are restricted to local effects or are subsequent to local effects. C(M)IT/MIT should be classified Xn; R21 'Harmful in contact with skin' according to the EU criteria for classification. (corr. to T; R24 'Toxic in contact with skin' for C(M)IT/MIT 3:1) according to the directive 67/548/EC. A classification as Acute Tox 3 / H312: Harmful in contact with skin is required according to the regulation 1272/2008/EC (corr. to Acute tox 2 / H 310: Fatal in contact with skin for C(M)IT/MIT 100 %).

After acute exposure by inhalation, C(M)IT/MIT induces effects in relation with its corrosive properties.
The 4-hr nose-only acute inhalation LC_{50} of C(M)IT/MIT in rats ranges from 1.23 to 2.36 mg/L air (corr. to 0.171 to 0.33 mg a.i/L air). The effects observed are consistent with the clinical signs of respiratory irritation. It is likely that the deaths resulted from excess fluids in the respiratory tract due to the irritant/corrosive nature of C(M)IT/MIT.
The studies from Dow and Thor result in a classification Xn; R20 'Harmful by inhalation' (corr. to T+; R26 'Very toxic by inhalation' for C(M)IT/MIT 3:1) according to the directive 67/548/EC. A classification as Acute Tox 4 / H332: Harmful if inhaled is required according to the regulation 1272/2008/EC (corr. to Acute tox 2 / H 330: Fatal if inhaled for C(M)IT/MIT 100 %).

Irritation/Sensitisation

C(M)IT/MIT is severely irritant to corrosive to the skin of rabbit in the different studies submitted. It should be classified as C; R34-Corrosive/Causes burns according to the EU criteria for classification with specific concentration limits: C ≥ 0.6% (C, R34) and 0.06% ≤ C < 0.6% (Xi, R36/38), according to the directive 67/548/EC. A classification as Skin Corr. 1C H 314: Causes severe skin burns and eye damage should be required due to the study results, however a harmonised classification as Skin Corr. 1B has been set, and therefore this classification is retained[5], Specific concentration limits: Skin Corr. 1B; H314: Causes severe skin burns and eye damage C ≥ 0.6%, according to the regulation 1272/2008/EC are proposed.

Due to the corrosivity of C(M)IT/MIT observed in the skin irritation studies, an eye irritation study was not deemed necessary since the substance has to be considered as to pose a risk of serious damage to the eyes.
The classification of the C(M)IT/MIT as corrosive includes the risk of severe damages to the eyes.

Regarding the irritation of airways, a concentration of 69 µg/l of Kathon 886F induced a 50% reduction in the respiratory rate in mice (RD50). C(M)IT/MIT should therefore be classified as Xi; R37-Irritating to respiratory system according to the directive 67/548/EC and STOT SE 3, H 335: May cause respiratory irritation according to the regulation 1272/2008/EC.

C(M)IT/MIT is a skin sensitizer according to a GPMT, a B · ler test, an open epicutaneous test and two LLNAs. A classification R43 – Sensitisation by skin contact is appropriate according to the directive 67/548/EC and Skin Sens. Cat 1A/ H317: May cause an allergic skin reaction according to CLP regulation, with specific concentration limit of 0.0015% (equivalent to 15 ppm) set during the meeting of the commission working group on the C&L of dangerous substances of 21 January 2000. This value will be used as a threshold value in a qualitative risk assessment for local effects by dermal route.

It is not possible to evaluate the potential of respiratory sensitisation as no studies addressing respiratory sensitisation of C(M)IT/MIT are available.

Repeated dose toxicity

- Oral studies

C(M)IT/MIT was tested in several oral repeated dose toxicity studies in rabbits, rats and dogs for 4 weeks and 3 months.
The major toxic effects observed were related to a gastric irritation. Decreases in body weight and in water intake were also reported after exposure to C(M)IT/MIT but were attributed to palatability. There was no evidence of systemic toxicity at the highest tested doses.
From the 90-day study in rats, a gastric irritation can be considered as a critical effect for setting a $NOAEC_{oral}$ at 536 ppm (corr. to 75 ppm a.i.) (w/v). In the absence of systemic effects, the NO(A)EL for systemic effects can be set at the highest tested dose (16.3 mg ai/kg bw/d).
From the 90-day study in dogs, in the absence of systemic and local effects, the NO(A)EL can be set at the highest tested dose (750 ppm ai, corr. to 22 mg ai/kg bw/d).
From the 4-week study in rabbits, a NOAEL at 27.9 mg/kg bw/d (corr. to 3.9 mg ai/kg.bw/d) based on mortality indirectly due to gastric irritation. There was no evidence of systemic toxicity at any dose level. A NOAEC of 2.9 mg/kg/day (corr. to 0.4 mg a.i./kg bw/d) based on the fundus irritation has been set.

[5] This classification may be revised in the CLH report.

From the 2-year study in rats, a NOAEL at 300 ppm a.i (corr. to 17.2 and 25.7 mg a.i/kg bw/d for males and females respectively) has been adopted based on no systemic effect observed. A NOAEC of 210 ppm (corr. to 30 ppm a.i) based on local irritation of the forestomach has been set.
In oral toxicity studies performed with metabolites of C(M)IT/MIT, NMMA (N-methyl malonamic acid) and MA (malonic acid), no treatment-related findings were noted up to the highest tested doses (500 ppm for NMMA and 100 ppm for MA).

- Dermal studies

Two 90-day dermal repeated dose toxicity studies were performed with C(M)IT/MIT in rabbit and rat. Local skin irritation, with erythema, edema and eschar formation, was the main topic toxic response to the tested substance.
In the 90-day dermal study in rabbit submitted by Dow, mortalities due to pulmonary complications appeared only in treated rabbits. It is difficult to appreciate the relevance of these effects; nevertheless, it seemed to be due to endemic respiratory disease, further aggraved by stress associated with dermal application of the corrosive tested substance. Furthermore, some histopathological finding in lung occurred variously in all groups, including control. These effects were not observed in a fully adequate study in rat submitted by Thor. Thus, the deaths were not attributed to a direct systemic effect of C(M)IT/MIT.
Additionally, the Dow study shows some methodological limitations: the tested substance was not analytically verified in the dosing solutions for concentration or stability and there were 6 animals/sex/group rather than the suggested 10/sex/group (OECD 411).
Therefore, considering the elements above, in the absence of any systemic effects, a $NOAEC_{dermal}$ of 0.1 mg/kg bw/d (corr. to 0.174% a.i.), based on skin reactions like erythema, edema and eschar has been adopted.
In the 30-month study in mice, no systemic effect was observed at necropsy.

- Inhalation studies

In a 90-day inhalation study, it was demonstrated that C(M)IT/MIT induces an irritation of the respiratory tract at the contact site with chromo-rhinorrhea, rhinorrhea, eye squint, bradypnea and dyspnea. Since only local effects have been identified, the NOAEC based on these effects is 2.4 mg/m^3 (corr. to 0.34 mg a.i./m^3).

Genotoxicity

- *In vitro* tests

Several *in vitro* studies of genotoxicity were performed with C(M)IT/MIT. Positive results were observed in three Ames assays and in three tests in mammalian cells (one chromosomal aberration test and two mouse lymphoma assays), with or without S9 activation. In contrast, C(M)IT/MIT was not mutagenic in primary culture of rat hepatocytes (UDS) and in a mouse cell transformation test.

A test was also performed with the major metabolite of C(M)IT/MIT, N-(methyl)malonamic acid (NMMA), which appeared not to be mutagenic when tested in a bacterial gene mutation assay test (Ames assay).

- *In vivo* tests

C(M)IT/MIT was tested in one *in vivo* chromosomal aberrations assay in mice (bone marrow) and one micronucleus test in mice (bone marrow). Negative results were observed in these in vivo studies.

In the studies on tissue distribution of radiolabel in mouse presented in the dossier for MIT and C(M)IT (referenced A6.2.a/03 and A6.2.b/03, respectively in the doc IIIA), radioactivity has been detected in bone marrow tissue following a single oral dose of the test material to adult male and female. This information provides support to the validity of the chromosome aberration test on bone marrow in mice and the micronuclei on bone marrow in mice, since it determines the extent of C(M)IT and MIT distribution to bone marrow of mice after oral exposure.

In the absence of genotoxicity, additional tests were carried out in tissue other than bone marrow. Two UDS assays in rats confirmed the absence of genotoxicity of C(M)IT/MIT when tested *in vivo*.

The overall conclusion from these studies is that C(M)IT/MIT cannot be considered as genotoxic.

Carcinogenicity

C(M)IT/MIT was tested in two chronic/carcinogenicity tests by either the oral route (rat) or dermal route (mouse). C(M)IT/MIT produced no evidence of carcinogenicity (ie., no treatment-related increase in the type or incidence of neoplasms in any group) up to the highest tested doses in these studies : 2 140 ppm in rat and 2860 ppm in mice (corr. to 300 ppm a.i. in rat and 400 ppm a.i. in mice).

Reproductive toxicity

- Developmental toxicity

C(M)IT/MIT was tested in two developmental toxicity studies in rats. None of them revealed a developmental toxicity in pups. In dams, irritating effects at gastric level were principally found, with effects on food consumption and body-weight gain. Based on the study submitted by Thor, the highest tested dose without maternal toxicity was 28.2 mg/kg/day (corr. to 3.95 mg a.i./kg/day). An apparent dose-related increase in mortality of dams was observed in the Dow's study but was eventually deemed as not treatment-related in the absence of mortality in the Thor's study and on the basis of the necropsy data (gross pathological examination showed red areas in the lungs indicating a wrong administration route).

One developmental study in rabbits is also available (Dow). It didn't reveal a developmental toxicity in pups. In dams, irritating effects at gastric level were principally found, with effects on food consumption and body-weight gain. The highest tested dose without maternal toxicity was 14 mg/kg/day (corr. to 2 mg a.i./kg/day).

- Fertility

When tested in both one-generation and two-generation reproductive toxicity studies in the rat, C(M)IT/MIT produced no evidence of reproductive toxicity including no effects on fertility/mating or on post-natal development at any dose.

Neurotoxicity

No studies were requested due to the absence of neurotoxicity alert in the repeated-dose toxicity studies.

Human data

Skin reactions (irritation, chemical burns and sensitisation) are widely reported from medical data but no epidemiological studies are available.
Due to the strong sensitising potential of C(M)IT/MIT, the skin exposure should be reduced as much as possible (closed systems, protective equipment,…)

2.2.1.3 Exposure assessment

Table 2.2.1-1: Exposure paths to C(M)IT/MIT

Exposure path	Industrial use	Professional use (application of biocidal product and use of preserved MWF)	General public (secondary exposure)	Via the Environment
Oral	No	No	No	Negligible
Dermal	Negligible/No	Yes	No	Negligible
Inhalation	Negligible/No	Yes	No	Negligible

Quantitative risk assessment was performed for both systemic effects and local effects (irritation), comparing the estimated exposure with relevant reference values (AECs/AELs). As the AEC for dermal local effect is expressed as ppm a.i., PPE for dermal protection can only be taken into account on a qualitative basis.

Acticide® 14 (14% C(M)IT/MIT) product from Thor and Kathon™ 886F (14% C(M)IT/MIT) product from Dow Chemical are both the technical grade of the active substance C(M)IT/MIT and the representative biocidal products for the use as metalworking-fluid (MWF) preservative (Product type 13). Nevertheless, The human exposure assessment is based on the active ingredient C(M)IT/MIT (3:1) at 100% i.e. without water and stabilizers, defined as C(M)IT/MIT a.i.

2.2.1.3.1 Professional exposure

⇒ **Primary exposure**

Scenario description and exposure determinants

Exposure estimates are performed in order to obtain a realistic upper limit exposure levels to C(M)IT/MIT a.i. when used in metalworking fluids. The initial in-use concentrations of the active substance are 35 ppm a.i. (w/w) for Kathon™ 886F (14% C(M)IT/MIT) and 42 ppm a.i. (w/w) for Acticide® 14 (14% C(M)IT/MIT).

There are three primary exposure task scenarios identified for the use of PT13 products:

1. Mixing and Loading: the biocidal product is added directly to the sump,
2. Application: the metalworking process itself involving operating the machines, handling objects wetted with MWF, and other daily tasks, such as cleaning the wetted tools and surfaces,
3. Post application (includes disposal): tasks involved include sump maintenance, fluid monitoring, disposal and recycling.

For each exposure scenario, Tier 1 exposure estimates are provided. Tier 2 assessments have been developed only when Tier 1 assessment leads to unacceptable risks. Tier 1 estimates assume no Personal Protective Equipment (PPE). Tier 2 estimates assume appropriate PPE and/or risk mitigation measures.
As the main effects of C(M)IT/MIT are local (e.g. irritation), external exposure for different routes is calculated:

- concentration of the active ingredient deposed on skin (ppm a.i.) for dermal exposure,
- concentration of active ingredient in the inhaled air (mg a.i. /m^3), during the tasks and as 8-hours time weighted average (8-hr-TWA).

PPE: the AEC for dermal local effect is expressed as ppm a.i., so PPE for local effect dermal protection will not decrease the concentration of exposure but the occurrence of the event of skin contact with the active ingredient. PPE for dermal protection will be taken into account on a qualitative basis during the risk assessment stage.

Mixing and loading

Metalworking fluid is preserved by administering the biocidal product to the metalworking fluid system. The mixing and loading tasks involve the removal of the product from its container and introduction to the metalworking fluid sump and may be conducted by automation or manually. In the automated process, the biocide is metered directly into the sump from a holding tank or other type of bulk container. The manual process involves a worker dispensing (via a tap or by pouring) a measured quantity of product into a jug and manually pouring the product into the sump. Manual pouring is considered a worst case scenario compared to the automated transfer. The exposure was assessed following this scenario.

The most relevant paths of exposure to C(M)IT/MIT during mixing/loading of the biocidal product are from the dermal and inhalation routes. The oral route is considered insignificant.

According to the recommendation by the Human Exposure Expert Group (HEEG) agreed in TM I 08 about mixing and loading task, the EUROPEOM II database (Professional pouring formulation from a container into a fixed receiving vessel) was used.

Application

The exposure of professional users during metalworking tasks (metalworking fluid with 35 ppm ai C(M)IT/MIT, worst case) was estimated according to the Technical Notes for Guidance (TNsG) on human exposure to biocidal products.

Metalworking machines and operations are of varying degrees of sophistication, but all require human intervention. Dermal exposure may occur through direct contact with fluid, articles and surfaces contaminated with fluid, and deposition from airborne aerosols. Exposure by inhalation occurs through airborne aerosols generated at the cutting head of metalworking machinery. The oral route is considered insignificant.

Metalworking professionals involved with tool setting and dismantling equipment, metalworking, and handling worked pieces typically utilize coveralls and face/eyes protection for these operations. Protective gloves may or may not be used for metalworking since gloves could be a safety hazard if worn near rotating machinery.

Duration and task frequencies are based on the HEEG opinion on MWF agreed at TMIII 08. Several models have been combined to assess exposure during metal working. The metal working model 2 from TNsG 2002 has been used for inhalation exposure. As this model does not contain dermal data it has been completed with the metal working model from BEAT which contains body exposure data and a worst case approach has been used to assess hands exposure considering an exposure to 6 ml/h of product as proposed in TNsG 2002.

Considering the dermal local effects, the use concentrations are respectively 35 ppm a.i. for Dow Chemical and 42 ppm a.i. for Thor GmbH.

Post-Application

The primary tasks involved in post-application activities include sump maintenance and fluid monitoring. Sump maintenance involves cleaning filters, removing tramp oil, swarf (shaving) removal and sump emptying. Fluid monitoring involves taking refractive index measurements and using dip slides to monitor bacterial contamination. Other tasks that would fall into this category include cleaning surfaces and equipments, collecting swarfs (shavings), used MWF and empty drums for recycling or disposal and transferring worked pieces to storage. Biocide concentrations of C(M)IT/MIT may vary for certain tasks.

These tasks can be done by operators involved in the application or by ancillary workers not involved in the application phase, so the exposure may be considered as secondary. Nevertheless, they are treated in this part to keep professional exposure together.

Duration and frequencies of these tasks are based on TNsG 2002. Exposures rates have been extrapolated from BEAT's model 'cleaning of spray equipment' as there is no specific model for such tasks.

A) Primary exposure to Kathon 886F (Dow chemical's product) for professionals

Table 2.2.1-2 : Summary of professional exposure estimates at metalworking facilities (Kathon 886F in-use dose of 35 ppm C(M)IT/MIT)

Tier	Inhalation exposure		Dermal exposure		Total exposure
PPE	External concentration	Systemic dose	Deposit on skin	Systemic dose	Systemic dose
	mg a.i. /m^3 air (8-hrs TWA)	mg a.i. / kg bw /day	ppm a.i.	mg a.i. / kg bw /day	mg a.i. / kg bw /day
Task – time frame :	**Professional diluting product into MWF (mixing/loading)**				
Tier 1: Without PPE	1.05×10^{-3}	1.75×10^{-4}	140 000	5.80×10^{-1}	5.81×10^{-1}
Tier 2: With gloves and impermeable coveralls	1.05×10^{-3}	1.75×10^{-4}	140 000	5.24×10^{-2}	5.25×10^{-2}
Task – time frame :	**Professional metalworking (application)**				
Tier 1: Without PPE	1.16×10^{-5}	1.93×10^{-6}	35	4.08×10^{-2}	4.08×10^{-2}
Task – time frame :	**Sump maintenance (post-application)**				
Tier 1: Without PPE	5.78×10^{-6}	9.63×10^{-7}	35	3.85×10^{-3}	3.85×10^{-3}
Task – time frame :	**Fluid monitoring (post application)**				
Tier 1: Without PPE	2.41×10^{-7}	4.01×10^{-8}	35	1.60×10^{-4}	1.60×10^{-4}

Combined professional exposure

The combined exposure scenario involves one worker conducting several tasks in the same work shift. The sump maintenance is excluded as it occurs only once a month and, due to its duration (4 hours), it is improbable that the same operator does sump maintenance and application phase on the same day. The resulting exposure estimates are based on a worker loading the biocidal product into the sump, metalworking and conducting post application (including cleaning and monitoring) activities all on the same day.

Concerning the local effects, as for local dermal effect it is the concentration of the C(M)IT/MIT during the event of contact that it is relevant, then combined exposure for local exposure has only been assessed for the inhalation route.

The inhalation external exposures and systemic doses values for each scenario were added in following tables to derive a combined exposure estimate for the scenario described above.

Table 2.2.1-3 : Combined professional exposure estimates to metalworking operator (Kathon 886F in-use dose of 42 ppm C(M)IT/MIT)

Tier 1 PPE : none assumed					
		Loading	Metal working	Monitoring	**TOTAL**
Total dermal exposure					
Systemic dose via skin	mg a.i./kg bw	5.80×10^{-1}	4.08×10^{-2}	1.60×10^{-4}	**6.21×10^{-1}**
Exposure by inhalation					
8hr-TWA concentration *	mg a.i./m^3	1.05×10^{-3}	1.16×10^{-5}	2.41×10^{-7}	**1.06×10^{-3}**
Systemic inhaled dose	mg a.i./kg bw	1.75×10^{-4}	1.93×10^{-6}	4.01×10^{-8}	**1.77×10^{-4}**
Total systemic dose	**mg a.i./kg bw**	**5.81×10^{-1}**	**4.08×10^{-2}**	**1.60×10^{-4}**	**6.22×10^{-1}**

*: Time-weighted average for 8-hour exposure duration.

Tier 2 loading + Tier 1 metal working and post-application Loading with PPE: chemical-resistant gloves and impermeable apron/coveralls					
		Loading	Metal working	Monitoring	**TOTAL**
Total dermal exposure					
Systemic dose via skin	mg a.i./kg bw	5.24×10^{-2}	4.08×10^{-2}	1.60×10^{-4}	**9.33×10^{-2}**
Exposure by inhalation					
8hr-TWA concentration *	mg a.i./m^3	1.05×10^{-3}	1.16×10^{-5}	2.41×10^{-7}	**1.06×10^{-3}**
Systemic inhaled dose	mg a.i./kg bw	1.75×10^{-4}	1.93×10^{-6}	4.01×10^{-8}	**1.77×10^{-4}**
Total systemic dose	**mg a.i./kg bw**	**5.25×10^{-2}**	**4.08×10^{-2}**	**1.60×10^{-4}**	**9.35×10^{-2}**

*: Time-weighted average for 8-hour exposure duration.

B) Primary exposure to acticide: 14 (Thor's product) for professional

Table 2.2.1-4 : Summary of professional exposure estimates at metalworking facilities (Acticide® 14 in-use dose 42 ppm a.i. C(M)IT/MIT)

Tier	Inhalation exposure		Dermal exposure		Total exposure
PPE	External concentration	Systemic dose	Deposit on skin	Systemic dose	Systemic dose
	mg a.i. /m^3 air (8-hrs TWA)	mg a.i. / kg bw /day	ppm a.i.	mg a.i. / kg bw /day	mg a.i. / kg bw /day
Task – time frame :	**Professional diluting product into MWF (mixing/loading)**				
Tier 1: Without PPE	1.26×10^{-3}	2.10×10^{-4}	140 000	6.97×10^{-1}	6.97×10^{-1}
Tier 2: With gloves and impermeable coveralls	1.26×10^{-3}	2.10×10^{-4}	140 000	6.28×10^{-2}	6.30×10^{-2}
Task – time frame :	**Professional metalworking (application)**				
Tier 1: Without PPE	1.39×10^{-5}	2.31×10^{-6}	42	4.90×10^{-2}	4.90×10^{-2}
Task – time frame :	**Sump maintenance (post-application)**				
Tier 1: Without PPE	6.93×10^{-6}	1.16×10^{-6}	42	4.62×10^{-3}	4.62×10^{-3}
Task – time frame :	**Fluid monitoring (post application)**				
Tier 1: Without PPE	2.89×10^{-7}	4.81×10^{-8}	42	1.93×10^{-4}	1.93×10^{-4}

Combined professional exposure

The combined exposure scenario involves one worker conducting several tasks in the same work shift. The sump maintenance is excluded as it occurs only once a month and, due to its duration (4 hours), it is improbable that the same operator does sump maintenance and application phase on the same day. The resulting exposure estimates are based on a worker loading the biocidal product into the sump, metalworking and conducting post application (including cleaning and monitoring) activities all on the same day.

As for local dermal effect it is the concentration of the C(M)IT/MIT during the event of contact that it is relevant, combined exposure have only been assessed for inhalation exposure.

The inhalation exposures for each scenario were added in following tables to derive a combined exposure estimate for the scenario described above.

Concerning the local effects, as for local dermal effect it is the concentration of the C(M)IT/MIT during the event of contact that it is relevant, then combined exposure for local exposure has only been assessed for the inhalation route.

Concerning the systemic effects, as a worst case approach the acute exposure for metal working and monitoring will be used. There are no differences for acute and chronic exposure concerning the mixing loading.

The inhalation external exposures and systemic doses values for each scenario were added in following table to derive a combined exposure estimate for the scenario described above.

Table 2.2.1-5 : Combined professional exposure estimates to metalworking operator (Acticide® 14 in-use dose 42 ppm a.i. C(M)IT/MIT)

Tier 1 PPE : none assumed					
		Loading	Metalworking	Monitoring	**TOTAL**
Total dermal exposure					
Systemic dose via skin	mg a.i./kg bw	6.97×10^{-1}	4.90×10^{-2}	1.93×10^{-4}	**7.46×10^{-1}**
Exposure by inhalation					
8hr-TWA concentration *	mg a.i./m^3	1.26×10^{-3}	1.39×10^{-5}	2.89×10^{-7}	**1.27×10^{-3}**
Systemic inhaled dose	mg a.i./kg bw	2.10×10^{-4}	2.31×10^{-6}	4.81×10^{-8}	**2.12×10^{-4}**
Total systemic dose	**mg a.i./kg bw**	**6.97×10^{-1}**	**4.90×10^{-2}**	**1.93×10^{-4}**	**7.46×10^{-1}**

*Time-weighted average for 8-hour exposure duration.

Tier 2 loading + Tier 1 application and monitoring Loading with PPE: chemical-resistant gloves and impermeable apron/coveralls					
		Loading	Metalworking	Monitoring	**TOTAL**
Total dermal exposure					
Systemic dose via skin	mg a.i./kg bw	6.28×10^{-2}	4.90×10^{-2}	1.93×10^{-4}	**1.12×10^{-1}**
Exposure by inhalation					
8hr-TWA concentration *	mg a.i./m^3	1.26×10^{-3}	1.39×10^{-5}	2.89×10^{-7}	**1.27×10^{-3}**
systemic inhaled dose	mg a.i./kg bw	2.10×10^{-4}	2.31×10^{-6}	4.81×10^{-8}	**2.12×10^{-4}**
Total systemic dose	**mg a.i./kg bw**	**6.30×10^{-2}**	**4.90×10^{-2}**	**1.93×10^{-4}**	**1.12×10^{-1}**

*Time-weighted average for 8-hour exposure duration.

⇒ **Secondary exposure**

Secondary exposure scenarios include cleaning surfaces and equipments, collecting shavings (swarf), used fluid and empty drums for recycling or disposal and transferring worked pieces to storage. Potential exposure to C(M)IT/MIT from these tasks is anticipated to be covered by the exposure during the mixing and loading and the application phases, as explained hereafter.

The daily cleaning and collecting tasks are included in the exposure assessment for the application phase. The exposure to residues on surfaces and objects is anticipated to be lower than the exposure by handling worked pieces and operating the machines.

The exposure during transfer of worked pieces to storage is negligible compared to application phase, as the residues of C(M)IT/MIT are intended to be removed by the degreasing of the pieces.

The empty containers containing residues of the concentrated product must be considered as dangerous wastes and handled very carefully according to the related regulations. Before cleaning or dismantling, the pumps and lines must be rinsed to insure a sufficient dilution. In these conditions, the exposure potential while handling or cleaning empty containers, product wastes and pumps is anticipated to be far less than those for the sump loading phase.

2.2.1.3.2 Non-professional exposure

As ACTICIDE 14 and Kathon 886 F are for professional use only, exposure of general population is not expected during use of treated metalworking fluids. Bystander exposure to metalworking fluids containing C(M)IT/MIT is also considered irrelevant since these operations are conducted in closed buildings with restricted access.

2.2.1.3.3 Ingestion of residues in food of animal origin

Not relevant.

2.2.1.4 Risk characterisation

Quantitative risk assessment was performed for both systemic and local effects by inhalation route (irritation), comparing the estimated exposure with relevant reference values (AELs/AECs). The Margin of Exposure (MOE) approach was used as well, comparing the critical NO(A)EL with the estimated exposure.
Concerning the local effects by dermal route, in order to take into account the sensitizing properties of the active ingredient, a qualitative risk assessment was performed comparing the exposure concentrations with the threshold value presented above (15 ppm a.i.).

AELs determination
According to the TNsG on Annex I Inclusion chapter 4.1 (Quantitative Risk Characterisation, September 2009), Acceptable Exposure Level (AELs) were derived for acute-, medium- and long –term exposures.
These AELs represent the internal (absorbed) dose available for systemic distribution from any route of absorption, and is expressed in mg ai/kg bw/d.

AEL = NO(A)EL * % absorption / assessment factors

An acute- and medium-term AEL can be derived from the 90-day toxicity study in dogs exposed through diet, where a NO(A)EL was identified at 750 ppm ai (corr. to 22 mg ai/kg bw/d) as no systemic effect was observed at the highest tested dose.
A long-term AEL can be derived from the carcinogenicity study in rats exposed through drinking water, where a NO(A)EL was identified at 300 ppm ai (corr. to 17.2 mg ai/kg bw/d) as no systemic effect was observed at the highest tested dose.

The critical studies used for the derivation of AELs were summarised in the table below.

Critical endpoints for the determination of AELs

Study	NO(A)EL	Effects at LO(A)EL
Acute and medium-term AELs		
90-day study in dogs (A6.4.1/02) (Thor)	22 mg ai/kg bw/d	none
Long-term AEL		
2-year study in rats (A6.5/01-A6.7/01) (Dow)	17.2 mg ai/kg bw/d	none

AEL approach

To translate the selected NOAEL into an AEL, the NOAEL is divided by the assessments factors (safety factors). Systemic AELs should be derived using a default factor of 100 corresponding to 10 for inter-species variation and 10 for intra-species variation and an oral absorption factor of 50%.

The following AELs were therefore derived:

- Acute/medium-term AEL= (22/100) x 50% = 0.11 mg ai/kg bw/d
- Long-term AEL= (17.2/100) x 50% = 0.09 mg ai/kg bw/d

In the AEL approach, a risk is considered acceptable if AEL > exposure.
In practice, exposure is expressed as a percentage of the AEL (%AEL).
The risk is therefore considered acceptable if %AEL < 100%.

MOE Approach

To translate the selected NOAEL into an MOE, the systemic NOAEL is divided by the exposure value.
A default factor of 100 corresponding to 10 for inter-species variation and 10 for intra-species variation will be used as reference margin of exposure (MOE_{ref}).

- If the MOE ≤ MOE_{ref}, the risk is not considered acceptable,
- If the MOE > MOE_{ref}, the risk is considered acceptable.

AECs determination

As local toxicity is considered as the critical endpoint associated with exposure, a qualitative approach with the threshold value of 15 ppm (specific concentration limit for sensitizing effect) will be used for dermal route. A quantitative approach will be realized for the inhalation route with the derivation of an Acceptable Exposure Concentrations (AECs); according to the guidance for Human Health Risk Assessment (Volume III, Part B, December 2013).
As well as for the AEL, the AEC corresponds to the NOAEC divided by the assessment factors.

AEC = NOAEC / assessment factors

C(M)IT/MIT induces irritation of the respiratory tract with chromo-rhinorrhea, rhinorrhea, eye squint, bradypnea, dyspnea after inhalation administration. The NOAEC of 0.34 mg ai/m^3/d from the 90-day toxicity study by inhalation route in rat was chosen for the derivation of the $AEC_{inhalation}$.

The critical studies used for the derivation of AEC were summarised in the table below.

Critical endpoints for the determination of the AECs

Study	NOAEC	Effects at LO(A)EL/LO(A)EC
Local effects (inhalation)		
90-day inhalation study in rats (A6.4.3/01)	0.34 mg ai/m^3	Irritation of the respiratory tract with chromo-rhinorrhea, rhinorrhea, eye squint, bradypnea, dyspnea

As far as only local effects were observed, a refined inter-species factor is directly proposed. It can actually be assumed that for a local effect at the port of entry, toxicokinetics do not contribute significantly to interspecies differences. In contrast, as the mechanism is not clearly known, it is prudent to assume that the toxicodynamic component should be kept at 2.5.
As well, it is assumed that toxicokinetic does not contribute significantly to intraspecies differences, therefore, this component can be reduced to 1. The intra-species assessment factor is therefore set at 3.2. An additional assessment factor of 2, accounting for the duration extrapolation from subchronic to chronic, is applied for deriving long-term inhalation AEC from medium-term studies.

These combined values (8 or 16) are used as reference margins of exposure (MOE_{ref}).

The following AECs were therefore derived for inhalation route:

- short/medium-term $AEC_{inhalation}$ = 0.34/8 = 0.04 mg a.i./m^3
- long-term $AEC_{inhalation}$ = 0.34/16 = 0.02 mg a.i. /m^3

Derivation of the ARfD (Acute Reference Dose)

The ARfD can be derived from the NOAEL of 2 mg ai/kg bw/d, based on decreased food consumption and decreased body weight gain (due to gastric irritation), determined in the developmental study in rabbits by applying an overall assessment factor of 100 (10 for interspecies variability and 10 for intraspecies variability).

ARfD = NOAEL/AF = 2/100 = **0.02 mg a.i./kg bw/d**

Derivation of the ADI (Acceptable Daily intake)

The ADI for C(M)IT/MIT can be derived from the NOAEC of 0.4 mg a.i./kg bw/d, based on gastric irritation, identified in the 28-days rabbit study, by applying an overall assessment factor of 100 (10 for interspecies variability and 10 for intraspecies variability). An additional assessment factor for extrapolating from sub-acute to chronic is considered not necessary since the chosen NOAEC is already a conservative value, the lowest of the data package.

ADI = NOAEL/AF = 0.4/100 = **0.004 mg/kg bw/d**

Local effects are concentration dependent, therefore for concentrations leading no gastric irritation, no ADI has to a taken into account.

2.2.1.4.1 Kathon 886F (Dow Chemical's Product)

Primary exposure scenarios for professionals

- **Quantitative risk assessment for systemic effects:**

	Total exposure (mg a.i/kg bw/d)	Relevant NOAEL (mg a.i./kg bw/d)	MOE_{ref} (sum of AFs)	MOE	AEL (mg a.i./kg bw/d)	%AEL
Task– time frame: Professional diluting product into MWF (mixing & loading) – once a week						
Tier 1 : Without PPE	5.81×10^{-1}	8.6	100	**15**	0.09	**645**
Tier 2: with gloves and impermeable coveralls	5.25×10^{-2}	8.6	100	164	0.09	58
Task – time frame: Professional metalworking (application) Direct Operating 480 min/day						
Tier 1: Without PPE	4.08×10^{-2}	8.6	100	211	0.09	45
Task – time frame: Sump maintenance (post-application) 240 min/day Once a month						
Tier 1: Without PPE	3.85×10^{-3}	8.6	100	2234	0.09	4.3
Task – time frame: Fluid monitoring (post-application) 10 min/day Once a week						
Tier 1: Without PPE	1.60×10^{-4}	8.6	100	53750	0.09	0.18

The risk characterisation for systemic exposure during the mixing and loading task is not acceptable in Tier 1, but is the risk became acceptable when PPE are worn with a MOE (164) higher than the MOE_{ref} (100) and a %AEL (58%) below 100%.
The risk for the application (professional metalworking) is acceptable in Tier 1 since the MOE (211) is higher than the MOEref and the %AEL (45%) is below 100%.
The risk for the sump maintenance is acceptable in Tier 1 since the MOE (2234) is higher than the MOEref and the %AEL (4.3%) is below 100%.
The risk for the fluid monitoring is acceptable in Tier 1 since the MOE (53750) is higher than the MOEref and the %AEL (0.18%) is below 100%.

- **Qualitative risk assessment for local effects**
  - **By dermal contact**

	Total exposure (ppm ai)	Threshold value (ppm a.i.)
Task– time frame : (mixing & loading) Once a week	**Dermal contact during the manual dilution of product into MWF**	
Tier 1 : Without PPE	140 000	15
Task – time frame: Direct Operating 60 min/day Others tasks 420 min/day	**Professional metalworking (application)**	
Tier 1: Without PPE	35	15
Task – time frame: 240 min/day Once a month	**Sump maintenance (post-application)**	
Tier 1: Without PPE	35	15
Task – time frame: 10 min/day Once a week	**Fluid monitoring (post-application)**	
Tier 1: Without PPE	35	15

As the threshold value is expressed as ppm, PPE for dermal protection will not decrease the concentration of exposure but the occurrence of the event of skin contact with the active substance. The concentrations of C(M)IT/MIT used for these exposure scenarios are above the concentration that would lead to sensitization (15 ppm a.i.).

However, this risk of skin sensitization from C(M)IT/MIT active substance is readily controllable through the use of proper risk mitigation measures when handling formulations. Besides, the use of concentrated formulations is restrained to professional operators, the occurrence of exposure should be considered as accidental and manageable as such. But, exposure to metalworking fluids (application phase) cannot be prevented with gloves since they could be a safety hazard if worn near rotating machinery. **In order to take into account the sensitizing properties of the C(M)IT/MIT, the product concentration of use in MWF must be reduced below the threshold value of 15 ppm a.i.**

Therefore, packaging, equipments and procedures, e.g. **automated dosing systems**, should be designed to prevent exposure as much as possible. Moreover, effective skin protection such as gloves, goggles, protective overalls and boots is required under all the identified scenarios for use of C(M)IT/MIT based products. MSDS and product use instructions shall inform the users of the potential risks and prevention measures.

By using adapted processes, protective equipments and respecting good professional practices, the exposure potential to C(M)IT/MIT based products can be avoided and the risk of adverse health effects can be reduced to an acceptable level.

An approval is therefore still possible, provided such risk mitigation measures are implemented.

- **Quantitative risk assessment for local effects**

- **By inhalation**

	Total exposure (mg ai/m^3)	Relevant NOAEC (mg ai/m^3)	MOE_{ref} (sum of AFs)	MOE	$AEC_{inhalation}$ (mg ai/m^3)	%AEC
Task– time frame : (mixing & loading) Once a week	**Dermal contact during the manual dilution of product into MWF**					
Tier 1 : Without PPE	1.05×10^{-3}	0.34	16	324	0.02	2.25
Task – time frame: Direct Operating 60 min/day Others tasks 420 min/day	**Professional metalworking (application)**					
Tier 1: Without PPE	1.16×10^{-5}	0.34	16	29 310	0.02	0.06
Task – time frame: 240 min/day Once a month	**Sump maintenance (post-application)**					
Tier 1: Without PPE	5.78×10^{-6}	0.34	16	58 824	0.02	0.03
Task – time frame: 10 min/day Once a week	**Fluid monitoring (post-application)**					
Tier 1: Without PPE	2.41×10^{-7}	0.34	16	14.1×10^{5}	0.02	1.2×10^{-3}

Whatever the scenario considered, the %AEC in the Tier 1 (without PPE) is lower than 100% for respiratory exposure and the MOE_{ref} (16). It confirms then that **the use of Kathon™ 886F during the manual mixing and loading, application, sump maintenance and monitoring without PPE is acceptable for respiratory exposure.**

- **Risk assessment for systemic effects during combined professional exposure**

The combined exposure scenario involves one worker conducting several tasks in the same work shift. The sump maintenance is excluded as it occurs only once a month and, due to its duration (4 hours), it is improbable that the same operator does sump maintenance and application phase on the same day. The resulting exposure estimates are based on a worker loading the biocidal product into the sump, metalworking and conducting post-application (including cleaning and monitoring) activities all on the same day.

	Total exposure (mg a.i/kg bw/d)	Relevant NOAEL (mg a.i./kg bw/d)	MOE_{ref} (sum of AFs)	MOE	AEL (mg a.i./kg bw/d)	%AEL
Tier 1 : Without PPE	6.22×10^{-1}	8.6	100	**14**	0.09	**691**
Tier 2a loading + Tier 1 for application and post-application*	9.35×10^{-2}	8.6	100	92	0.09	**104**
Tier 2b loading with RMM against local effects + Tier 1 for application and monitoring**	4.12×10^{-2}	8.6	100	209	0.09	46

*: Loading PPE: chemical-resistant gloves and impermeable apron/coveralls
**: Taking into account PPE and RMM against local effect no systemic exposure during loading is considered.

The risk characterisation for combined systemic exposure identified an unacceptable risk in Tier 1. The risk became acceptable when PPE (chemical-resistant gloves and impermeable coveralls) are worn and RMM against local effects, such automated dosage, are applied, in order to avoid exposure during the loading task (tier 2b). When PPE and RMM for local effect are taken into account, no systemic exposure during loading is considered.
A MOE (209) higher than the MOE_{ref} (100) and a %AEL (46%) below 100% are calculated.

Secondary exposure for professionals

First, as stated previously, the secondary exposure for professionals potential secondary exposure to C(M)IT/MIT is anticipated to be covered by the exposure during the mixing and loading and the application phases, as explained hereafter.

The daily cleaning and collecting tasks are included in the exposure assessment for the application phase. The exposure to residues on surfaces and objects is anticipated to be lower than the exposure by handling worked pieces and operating the machines.

Finally, the exposure potential while handling or cleaning empty containers, product wastes and pumps is anticipated to be far less than those for the sump loading phase that must be below the threshold value of 15 ppm a.i. to prevent from sensitization.

Then no risk characterisation has been performed for the secondary exposure for professionals.

Non-professionals exposure

As Kathon 886F use is restricted to professional use only, exposure of general population is not expected during use of treated metalworking fluids. Bystander exposure to metalworking fluids containing C(M)IT/MIT is also considered irrelevant since these operations are conducted in closed buildings with restricted access.

Combined exposure

Combined exposure is not relevant in this assessment because consumers are not exposed to metalworking fluids and the exposure estimates for humans via the environment are insignificant when compared to estimates for workplace or occupational exposure.

2.2.1.4.2 Acticide 14 (Thor GmbH Product)

Primary exposure scenarios for professionals

- **Quantitative risk assessment for systemic effects**

	Total exposure (mg a.i/kg bw/d)	Relevant NOAEL (mg a.i./kg bw/d)	MOE_{ref} (sum of AFs)	MOE	AEL (mg a.i./kg bw/d)	%AEL
Task– time frame :	**Professional diluting product into MWF (mixing & loading) – once a week**					
Tier 1 : Without PPE	6.97×10^{-1}	8.6	100	**13**	0.09	**774**
Tier 2: with gloves and impermeable coveralls	6.30×10^{-2}	8.6	100	136	0.09	70
Task – time frame: Direct Operating 480 min/day	**Professional metalworking (application)**					
Acute Tier 1: Without PPE	4.90×10^{-2}	8.6	100	176	0.09	54
Task – time frame: 240 min/day Once a month	**Sump maintenance (post-application)**					
Acute Tier 1: Without PPE	4.62×10^{-3}	8.6	100	1862	0.09	5.1
Task – time frame: 10 min/day Once a week	**Fluid monitoring (post-application)**					
Acute Tier 1: Without PPE	1.93×10^{-4}	8.6	100	44560	0.09	0.2

The risk characterisation for systemic exposure during the mixing and loading task is not acceptable in Tier 1, but is the risk became acceptable when PPE are worn with a MOE (136) higher than the MOE_{ref} (100) and a %AEL (70%) below 100%.
The risk for the application (professional metalworking) is acceptable in Tier 1 exposure since the MOE (respectively 176) is higher than the MOEref and the %AEL (54%) is below 100%.
The risk for the sump maintenance is acceptable in Tier 1 exposure since the MOE (respectively 1862) is higher than the MOEref (100) and the %AEL (5.1%) is below 100%.
Finally, the risk for the fluid monitoring is acceptable for Tier 1 exposure since the MOE (44560) is higher than the MOEref (100) and the %AEL (0.2%) is below 100%.

- **Qualitative risk assessment for local effects**
  - By dermal contact

	Total exposure (ppm ai)	Threshold value (ppm a.i.)
Task – time frame: Professional metalworking (application) Direct Operating 60 min/day Others tasks 420 min/day		
Tier 1: Without PPE	42	15
Task – time frame: Sump maintenance (post-application) 240 min/day Once a month		
Tier 1: Without PPE	42	15
Task – time frame: Fluid monitoring (post-application) 10 min/day Once a week		
Tier 1: Without PPE	42	15

As the threshold value is expressed as ppm, PPE for dermal protection will not decrease the concentration of exposure but the occurrence of the event of skin contact with the active substance. The concentrations of C(M)IT/MIT used for these exposure scenarios are above the concentration that would lead to sensitisation (15 ppm a.i.).

However, this risk of skin sensitization from C(M)IT/MIT active substance is readily controllable through the use of proper risk mitigation measures when handling formulations. Besides, the use of concentrated formulations is restrained to professional operators, the occurrence of exposure should be considered as accidental and manageable as such. But, exposure to metalworking fluids (application phase) cannot be prevented with gloves since they could be a safety hazard if worn near rotating machinery. **In order to take into account the sensitizing properties of the C(M)IT/MIT, the product concentration of use in MWF must be reduced below the threshold value of 15 ppm a.i.**

Therefore, packaging, equipments and procedures, e.g. **automated dosing systems**, should be designed to prevent exposure as much as possible. Moreover, effective skin protection such as gloves, goggles, protective overalls and boots is required under all the identified scenarios for use of C(M)IT/MIT based products. MSDS and product use instructions shall inform the users of the potential risks and prevention measures.

By using adapted processes, protective equipments and respecting good professional practices, the exposure potential to C(M)IT/MIT based products can be avoided and the risk of adverse health effects can be reduced to an acceptable level.

An approval is therefore still possible, provided such risk mitigation measures are implemented.

- **Quantitative risk assessment for local effects**
  - By inhalation route

	Total exposure (mg ai/m^3)	Relevant NOAEC (mg ai/m^3)	MOE_{ref} (sum of AFs)	MOE	$AEC_{inhalation}$ (mg ai/m^3)	%AEC
Task– time frame : (mixing & loading) Once a week	**Inhalation exposure during the manual dilution of product into MWF**					
Tier 1 : Without PPE	1.26×10^{-3}	0.34	16	270	0.02	6.3
Task – time frame: Direct Operating 480 min/day	**Professional metalworking (application)**					
Tier 1: Without PPE	1.39×10^{-5}	0.34	16	24 460	0.02	0.07
Task – time frame: 240 min/day Once a month	**Sump maintenance (post-application)**					
Tier 1: Without PPE	6.93×10^{-6}	0.34	16	49 062	0.02	0.03
Task – time frame: 10 min/day Once a week	**Fluid monitoring (post-application)**					
Tier 1: Without PPE	2.89×10^{-7}	0.34	16	11.8×10^5	0.02	1.4×10^{-3}

Since the %AEC in the Tier 1 (without PPE) is less than 100% for respiratory exposure, the estimated exposure concentration is under the acceptable concentration. Likewise, the MOE (270) is higher than the MOE_{ref} (16), it confirms then that **the use of Acticide 14 during the manual mixing and loading without PPE is acceptable for respiratory exposure.**

Since the %AEC (0.07%) in the Tier 1 (without PPE) is less than 100% for respiratory exposure, the estimated exposure concentration is below the acceptable concentration. Likewise, the MOE (24460) is higher than the MOE_{ref} (16), it confirms then that **the use of Acticide 14 during use in MWF without PPE is acceptable for respiratory exposure.**

Since the %AEC (0.03%) in the Tier 1 (without PPE) is less than 100% for respiratory exposure, the estimated exposure concentrations for both acute and chronic exposure are below the acceptable concentration. Likewise, the MOE (49 062) is higher than the MOE_{ref} (16), it confirms then that **the use of Acticide 14 during the sump maintenance without PPE is acceptable for respiratory exposure.**

Since the %AEC ($1.4x10^{-3}$%) in the Tier 1 (without PPE) is less than 100% for respiratory exposure, the estimated exposure concentrations for both acute and chronic exposure are below the acceptable concentration. Likewise, the MOE (11.8×10^5) is higher than the MOE_{ref} (16), it confirms then that **the use of Acticide 14 during the fluid monitoring without PPE is acceptable for respiratory exposure.**

- **<u>Risk assessment for systemic effects during combined professional exposure</u>**

The combined exposure scenario involves one worker conducting several tasks in the same work shift. The sump maintenance is excluded as it occurs only once a month and, due to its duration (4 hours), it is improbable that the same operator does sump maintenance and application phase on the same day. The resulting exposure estimates are based on a

worker loading the biocidal product into the sump, metalworking and conducting post application (including cleaning and monitoring) activities all on the same day.

	Total exposure (mg a.i/kg bw/d)	Relevant NOAEL (mg a.i./kg bw/d)	MOE_{ref} (sum of AFs)	MOE	AEL (mg a.i./kg bw/d)	%AEL
Tier 1 : Without PPE	7.46×10^{-1}	8.6	100	**12**	0.09	**829**
Tier 2a loading + Tier 1 for application and monitoring*	1.12×10^{-1}	8.6	100	77	0.09	125
Tier 2b loading with RMM against local effects + Tier 1 for application and monitoring**	4.94×10^{-2}	8.6	100	174	0.09	55

*: Loading PPE: chemical-resistant gloves and impermeable apron/coveralls
**: Taking into account PPE and RMM against local effect no systemic exposure during loading is considered.

The risk characterisation for combined systemic exposure identified an unacceptable risk in Tier 1. The risk became acceptable when PPE (chemical-resistant gloves and impermeable coveralls) are worn and RMM against local effects, such automated dosage, are applied, in order to avoid exposure during the loading task (tier 2b). When PPE and RMM for local effect are taken into account, no systemic exposure during loading is considered. A MOE (174) higher than the MOE_{ref} (100) and a %AEL (55%) below 100% are calculated.

Secondary exposure for professionals

Secondary exposure scenarios include cleaning surfaces and equipments, collecting shavings (swarf), used fluid and empty drums for recycling or disposal and transferring worked pieces to storage. Potential exposure to C(M)IT/MIT from these tasks is anticipated to be covered by the exposure during the mixing and loading and the application phases, as explained hereafter.
The daily cleaning and collecting tasks are included in the exposure assessment for the application phase. The exposure to residues on surfaces and objects is anticipated to be lower than the exposure by handling worked pieces and operating the machines.
The exposure during transfer of worked pieces to storage is negligible compared to application phase, as the residues of C(M)IT/MIT are intended to be removed by the degreasing of the pieces.
The empty containers containing residues of the concentrated product must be considered as dangerous wastes and handled very carefully according to the related regulations.

Before cleaning or dismantling, the pumps and lines must be rinsed to insure a sufficient dilution. In these conditions, the exposure potential while handling or cleaning empty containers, product wastes and pumps is anticipated to be far less than those for the sump loading phase that must be below the threshold value of 15 ppm a.i. to prevent from sensitization.

Non-professionals exposure

As Acticide 14 use is restricted to professional use only, exposure of general population is not expected during use of treated metalworking fluids. Bystander exposure to metalworking fluids containing C(M)IT/MIT is also considered irrelevant since these operations are conducted in closed buildings with restricted access.

Combined exposure

Combined exposure is not relevant in this assessment because consumers are not exposed to metalworking fluids and the exposure estimates for humans via the environment are insignificant when compared to estimates for workplace or occupational exposure.

2.2.1.5 Overall conclusion on risk characterisation for metalworking fluids products

The active substance (3:1 ratio mixture of C(M)IT/MIT) and formulated product are manufactured in closed processes. Potential exposure to the small number of workers involved in production and/or formulation may occur during product sampling, packaging, equipment cleaning and sample analysis. Routine human contact with C(M)IT/MIT, excluding accidental exposure, does not occur because of the closed nature of the production/formulation process, because the workers are well informed and trained regarding the hazards and risks of the active substance, and appropriate engineering controls and good industrial hygiene practices are implemented.

The workers, which are using biocidal products in PT13 applications, are well informed about potential health hazards of chemicals used to formulate biocidal concentrate products, well trained for working with hazardous chemicals and routinely wear personal protective equipment. Additionally, good engineering controls and industrial hygiene practices are implemented in these plants, therefore, the potential for worker exposure to C(M)IT/MIT is very limited. The risk during the production/formulation of the biocidal products has not been assessed in this dossier, as it is not in the scope of the Directive 98/8/EC.

C(M)IT/MIT is a skin irritant and has skin sensitization potential. In rare situations where exposure to the a.s. may occur (accidental spills, etc.) plant workers must wear the appropriate personal protective equipment (PPE) to prevent over-exposure and to avoid any potential for skin/respiratory irritation or skin sensitisation.

If appropriate PPE is utilized while handling concentrated biocidal products during formulation, mixing/loading and post application tasks, the exposure concentration is not reduced but only the probability of occurrence. However, the exposure to concentrated products should be prevented.

Therefore, as the product is classified and labelled as corrosive (Kathon^{TM} 886F only) and sensitising, C(M)IT/MIT has to be handled with sufficient risk mitigation measures. Manual mixing and loading of KathonTM 886F and ACTICIDE 14 to metal working fluid presents an unacceptable risk for systemic effects, taking into account combined exposure. However, it is concluded that with automated systems of mixing and loading of KathonTM 886F and ACTICIDE 14, leading to avoid exposure during this task, the complete process, including all tasks presents an acceptable risk for systemic effects. But, exposure to metalworking fluids (application phase) cannot be prevented with gloves since they could be a safety hazard if worn near rotating machinery. **In order to take into account the sensitizing properties of the C(M)IT/MIT, the product concentration of use in MWF must be reduced below the threshold value of 15 ppm a.i. in the case of manual system.**

Therefore, the RMS considers that biocidal products containing up to 14% C(M)IT/MIT can be used in MWF applications provided that appropriate risk mitigation measures are applied during the loading of the products and the cleaning of the dispensing pumps. Possible measures (not exhaustive list) are:

- The containers of the products are designed to prevent spillages during pouring,
- Automated systems preventing contacts with the product are used for mixing and loading,
- Procedures are implemented to prevent contacts and spillages,
- Chemical-resistant coveralls, gloves, shoes and face-mask are worn during the mixing and loading phase,
- Use is restricted to operators informed of the hazards and formed for safe handling of the products.

Labels, MSDS and use instructions of the products shall inform the users of the hazards and of the protective measures. Written procedures and protective equipments shall be available at the places where the products are handled. The RMMs are summarised in the table below.

In conclusion, the use of C(M)IT/MIT as PT13 can be considered as safe for human health on the basis of the available data, provided adequate risk mitigation measures are implemented for avoiding dermal primary exposure.

Table 2.2.1-6: Primary Exposure – Use of the concentrated product Kathon™886F (Mixing and Loading)

Hazard			Exposure							Risk
Hazard Category	Effects in terms of C&L	Additional relevant hazard information	PT	Who is exposed?	Tasks, uses, processes	Potential exposure route	Frequency and duration of potential exposure	Potential degree of exposure	Relevant RMM&PPE	Conclusion on risk
Manual dilution of product into MWF (mixing & loading)										
High	Skin Corr 1B (H314) Skin Sens 1A (H317)	-	13	Industrial and professional users	The biocidal product (14% a.s.) is added directly to the sump	Skin	Once per week	<u>Manual loading:</u> Small exposure to spills <u>Semi automated and fully automated loading systems:</u> Accidental exposure to spills during connection of container to the pumping system	**Organizational RMM** • Restriction of manual loading to only small quantities. High quantities should be restricted to semi-automated or automated processes. **Personal protective equipment** • Respiratory protection: Wear respiratory protection if ventilation is inadequate. Combination filter for gases/vapours of organic, inorganic, acid inorganic and alkaline compounds (e.g. EN 14387 Type ABEK). • Hand protection: Suitable chemical resistant safety gloves (EN 374) also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374): E.g. nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm), butyl rubber (0.7 mm) and other	Acceptable: + Low frequency; + Minimization of manual phases; + Professionals using PPE; + Professionals following instructions for use; + Good standard of personal hygiene.

									Manufacturer's directions for use should be observed because of great diversity of types. • Eye protection: Tightly fitting safety goggles (splash goggles) (e.g. EN 166) • Body protection: Chemical protection clothes type 6 (eg EN 13034) **General safety and hygiene measures** Do not inhale gases/vapours/aerosols. Avoid contact with the skin, eyes and clothing. Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. When using, do not eat, drink or smoke. Hands and/or face should be washed before breaks and at the end of the shift. At the end of the shift the skin should be cleaned and skin-care agents applied. Gloves must be inspected regularly and prior to each use. Replace if necessary (*e.g.*, pinhole leaks).	

Table 2.2.1-7: Primary exposure – Use of the diluted product Kathon™886F (35 ppm) or ACTICIDE 14 (42 ppm) (Application and Post-application)

Hazard			Exposure							Risk
Hazard Category	Effects in terms of C&L	Additional relevant hazard information	PT	Who is exposed?	Tasks, uses, processes	Potential exposure route	Frequency and duration of potential exposure	Potential degree of exposure	Relevant RMM&PPE	Conclusion on risk
Professional metalworking (application)										
High	Skin Sens 1A (H317)	-	13	Industrial and professional users	The metalworking process itself involving operating the machines, handling objects wetted with MWF, and other daily tasks, such as cleaning the wetted tools and surfaces	Skin	daily	Direct contact with contaminated objects or residues during tool setting	**See table below for more details of the applicant proposal** **Personal protective equipment** • Hand protection: Suitable chemical resistant safety gloves (EN 374) also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374): E.g. nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm), butyl rubber (0.7 mm) and other Manufacturer's directions for use should be observed because of great diversity of types. • Body protection: Chemical protection clothes type 6 (eg EN 13034) at minimum for maintenance **General safety and hygiene measures**	Acceptable: + Minimization of manual phases; + Professionals using PPE when possible*; + Reduction of the product concentration of use below the threshold value of 15 ppm; + Professionals following instructions for use; + Good standard of personal hygiene.

									Do not inhale gases/vapours/aerosols. Avoid contact with the skin, eyes and clothing. Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. When using, do not eat, drink or smoke. Hands and/or face should be washed before breaks and at the end of the shift. At the end of the shift the skin should be cleaned and skin-care agents applied. Gloves must be inspected regularly and prior to each use. Replace if necessary (*e.g.*, pinhole leaks).	
Sump maintenance and Fluid monitoring (post-application)										
High	Skin Sens 1A (H317)	-	13	Industrial and professional users	Post application phases including sump maintenance, fluid monitoring, disposal and recycling	Skin	Once a month or once a week	<u>Maintenance:</u> direct contact with residues <u>Fluid monitoring:</u> accidental contact with spills	**Organisational RMM** Rinsing of the system before opening and cleaning. **Personal protective equipment** • Hand protection: Suitable chemical resistant safety gloves (EN 374) also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374): E.g. nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm), butyl rubber (0.7 mm) and other Manufacturer's directions for use should be observed because of great diversity of types. • Eye / face protection: Tightly fitting safety goggles (splash	Acceptable: + Professionals using PPE; + Professionals following instructions for use; + Good standard of personal hygiene.

									goggles) (e.g. EN 166) or face shield could be needed for maintenance • Body protection: Chemical protection clothes type 6 (eg EN 13034) at minimum for maintenance **General safety and hygiene measures** Do not inhale gases/vapours/aerosols. Avoid contact with the skin, eyes and clothing. Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. When using, do not eat, drink or smoke. Hands and/or face should be washed before breaks and at the end of the shift. At the end of the shift the skin should be cleaned and skin-care agents applied. Gloves must be inspected regularly and prior to each use. Replace if necessary (*e.g.*, pinhole leaks).	

* Exposure to metalworking fluids (application phase) cannot be prevented with gloves since they could be a safety hazard if worn near rotating machinery.

Applicant's RMMs proposal for PT13

	RMM PT13 (metal working)	**Scenario**	**Efficiency***
1	- automated/closed system - PPE (for maintenance)	Closed system. Continuous metal working for 2-5 days in an automated drilling process with continuous feed from large MWF systems. Chemical resistant gloves provide 100% protection during manual tasks (quality control, cleaning and maintenance).	High level of containment. No worker exposure to rotating machinery, i.e. the use of gloves is acceptable. No worker exposure to MWF.
2	- automated/semi-closed system - LEV - PPE (for maintenance)	Semi-closed system with LEV. For drilling for less than a work shift automated metal working is temporarily shielded in CNC cabinet. Workers are protected from splashes and aerosol by shielding and LEV. Chemical resistant gloves provide 100% protection during manual tasks (quality control, cleaning and maintenance).	No worker exposure to rotating machinery, i.e. the use of gloves is acceptable. Efficient shielding of worker against exposure to MWF.
3	- workplace separation - automated feed of MWF - forced ventilation in the work place. - PPE (for maintenance)	For drilling for less than a work shift automated metal working is shielded/separated to protect worker from splashes and aerosols with limited efficiency.	No worker exposure to rotating machinery, i.e. option to use gloves. Protection against inhalative and dermal exposure to MWF aerosol is limited.
4	- work organization - automated feed of MWF - forced ventilation in the work place. - Concentration of biocide in MWF has to be controlled.	Open metal working. Worker is trained not to be present in the workplace during metal working. PPE, e.g. chemical resistant gloves, provide protection during manual tasks (quality control, cleaning and maintenance).	No worker exposure to rotating machinery, i.e. option to use gloves. Duration of exposure to MWF aerosols is limited by means of organisation, training and PPE.
5	- use concentration of biocide in MWF has to be controlled, i.e. <15ppm. - forced ventilation in the	Manual metal working in open systems. Occasionally, worker is manually feeding MWF onto the rotating drill by means of a brush. For these open metal working no fluid circuit of	Limited worker exposure to rotating machinery. exposure with MWF aerosols is limited due to low amount used per event and short duration of using MWF (non-economic)

	work place. - working time limits	MWF is assumed (MWF is spend at once). PPE, e.g. chemical resistant gloves, provide protection during manual tasks (quality control, cleaning and maintenance).	

*: ECHA, Guidance for Human Health Risk Assessment, V.1 Dec 2013: Table 3, p337.

2.2.2 Environment risk assessment

2.2.2.1 Fate and distribution in the environment

2.2.2.1.1 Hydrolysis as a function of pH

In the environmental conditions (12°C, pH7), C(M)IT and MIT are considered as stable. C(M)IT and MIT are considered as hydrolytically stable in the test conditions at pH 4, 5 and 7. However at pH 9, C(M)IT hydrolyses at a moderate rate with an extrapolated half-life of 47.81 (Dow Chemical) – 120.6 (Thor) days at 12°C whereas MIT remains stable to hydrolysis.

2.2.2.1.2 Photolysis in water

C(M)IT and MIT photodegrade in water and natural sunlight at a moderate rate with half-lives of 6.6 and 18.2 days, respectively for C(M)IT and MIT.

2.2.2.1.3 Photolysis in air

C(M)IT and MIT photodegrade quickly with a highest DT50 of 17.5 hours for C(M)IT. The DT50 for MIT corresponds to 16.6 hours. Due to very low production and usage volume, the effect from C(M)IT, MIT and its potential photodegradation products towards global warming is minimal. Therefore, C(M)IT, MIT and its photodegradation metabolites impose no effect to global warming.

2.2.2.1.4 Biodegradation

In the Dow Chemical dossier, the ready biodegradation of the active substance was studied in separate tests for C(M)IT and MIT. C(M)IT is classified readily biodegradable with a failure of the 10-day window and MIT is classified as not readily biodegradable according to the criteria of the test, although significant biodegradation occurred. In the Thor dossier, adaptation of the inoculum used in the ready biodegradation test cannot be excluded and C(M)IT/MIT is therefore considered as not readily biodegradable.
Nevertheless, the biotic degradation of C(M)IT and MIT appears as the major metabolic pathway in simulation tests compared to abiotic degradation which is less rapid than biodegradation.
For the risk assessment, available STP simulation results for C(M)IT and MIT were considered. For C(M)IT, results show that no parent compound was detected in the effluent phase or in the sludge, C(M)IT was considered to be totally degraded in the STP and no emission of this compound in the different environmental compartments from the STP was foreseen. The only compound considered at the outlet of the STP was MIT. The fractions of MIT emission directed to water through effluents from the STP were 12.2% of MIT. No quantification of MIT in sludge has been carried out. Nevertheless, 6.6% of not identified radioactivity were detected in the sludge, and considered as MIT in a worst case approach. Besides, the half life of MIT has been determined to be 0.04 days.

Provided simulation studies were carried out on C(M)IT and MIT separately. Half life derived for MIT were harmonised with the values available in the MIT dossier by Slovenia. When necessary, other half life have been derived according to FOCUS recommendations leading to different half life for PEC calculations and for persistency assessment when simple first order do not apply to the experimental data. Additionally, in some aquatic studies, two concentrations of chemicals were tested, leading sometimes to observed toxicity. In this case two half live have been derived for the considered compartment. All these values were reported in the table below.

PBT assessment, DT50, 12°C			
Compartment	**C(M)IT**	**MIT**	**C(M)IT/MIT**
Water sediment	2.22 d	2.21 d	2.22 d
Estuarine (<20 µg/L)	1.49 d	2.63 d	2.63 d
Estuarine (>20µg/L)	5.82 d		5.82 d
Marine (<10 µg/L)	3.4 d (4.3 d at 9°C)	6.3 d (8.0 d at 9°C)	6.3 d (8.0 d at 9°C)
Marine (>10µg/L)	32.8 d (41.7 d at 9°C)	23.3 d (29.7 d at 9°C)	32.8 d (41.7 d at 9°C)
Soil	0.21 d	0.51 d	0.51 d
PEC calculation, DT50, 12°C			
Compartment	**C(M)IT**	**MIT**	**C(M)IT/MIT**
Estuarine (<20 µg/L)	1.49 d	2.63 d	2.63d
Estuarine (>20µg/L)	5.82 d		5.82 d
Marine (<10 µg/L)	3.4 d (4.3 d at 9°C)	15.7 d (20.0 d at 9°C)	15.7 d (20.0 d at 9°C)
Marine (>10µg/L)	32.8 d (41.7 d at 9°C)	23.3 d (29.7 d at 9°C)	32.8 d (41.7 d at 9°C)
Soil	1.48 d	0.51 d	1.48 d

In aquatic compartment, no biodegradation test in fresh water was provided by both applicants. Thus, estuarine water was considered as realistic worst case for biodegradation in fresh water. Indeed, for a same range of tested concentration, biodegradation estuarine water, with a lower salinity than marine water, was faster than the biodegradation in marine water and probably slightly higher than in fresh water. Half life in the water sediment system are provided for the whole system which appears as relevant considering the low adsorption capacities of C(M)IT and MIT. This is confirmed in In the water sediment studies in the Thor dossier, where similar half life are observed for the whole system and the water compartment. , which is consistent with low adsorption capacities of C(M)IT and MIT. Half life derived from the water sediment studies are in the same range than half life from the estuarine studies. In soil, C(M)IT and MIT rapidly dissipate following a biphasic kinetic. However, higher degradation rates are observed during the first 48h of the studies (sometimes less than 2 days, Dow chemical) and after this first rapid degradation, slower degradation rates are observed. Half lives are determined with a value of 1.48 days at 12°C for C(M)IT and a value of 0.51 day at 12°C for MIT.

2.2.2.1.5 Distribution

In adsorption tests, C(M)IT and MIT are weakly adsorbed to soil and activated sludge with Koc values less than 310 for Ka_{oc} and less than 421 for Kd_{oc}. This indicates that in sewage treatment plant, the active substance would probably be predominant in the water phase. If present in surface water, C(M)IT and MIT will partition mostly in the water column and will probably not accumulate in sediments. In soil, C(M)IT and MIT may have a potential for leaching, but the quick biodegradation of the substances in soil observed in the first 48 h of the biodegradation test in the Dow chemical dossier (half life <2 days) and the similar

results reported in the Thor Dossier indicate the risk for groundwater should be low. The Koc values used for risk assessment are 83.2 L/kg for C(M)IT and 7.5 L/kg for MIT (arithmetic mean).

2.2.2.1.6 Metabolites

Identification of metabolites was only carried out in the Dow Chemical Dossier. In the environment, C(M)IT and MIT rapidly dissipate to compounds which are in turn quickly biodegraded, indicating that persistence in the environment should be minimal. Among the principal metabolites of C(M)IT/MIT, a key metabolite has been identified and tested: N-methyl malonamic acid. It has been shown experimentally to be ready biodegradable. The other degradation products are all transient, reach their peak concentration in the first sampling times and quickly become less than 10% of applied radioactivity, generally after 5 to 10 days and in all cases by day 30. To confirm this, QSARs are conducted on these compounds and confirmed these metabolites are expected to be quickly biodegraded.

2.2.2.1.7 Accumulation

With a log Kow value for C(M)IT and MIT below 3 (log Kow = 0.401, C(M)IT –Dow Chemical), the potential of bioaccumulation or biomagnification of C(M)IT and MIT could be considered as negligible. Measured bioconcentration factor for C(M)IT was ≤ 54 which confirms that the bioconcentration potential of C(M)IT/MIT is very low. Furthermore according to the toxicokinetics, metabolism and distribution data provided in the toxicological section (2.2.1), the active substance is rapidly and extensively metabolized and is not considered to have an accumulative potential in food chain. At last, based on log Kow values, metabolites identified in the simulation studies are expeted to have a low potential of bioaccumulation.

2.2.2.2 Effects assessment on environmental organisms (active substance)

For each environmental compartment, the PNECs for active ingredient C(M)IT/MIT are presented in this section. Furthermore, as the risk assessment for the environment is almost based on MIT when releases to STP are considered, the PNECs for active ingredient MIT issued from the MIT dossier evaluated by Slovenia are also indicated in this section. Experimental data and QSAR have been provided for the metabolites which have been identified in simulation studies and are reported in document IIA. These data indicate that metabolites are less toxic than parent substance.

2.2.2.2.1 Aquatic compartment (including water, sediment and STP)

Aquatic organisms

Available valid aquatic ecotoxicological data provided by the two applicants (Dow Chemical and Thor) have been used to derive the PNEC for the aquatic (freshwater) compartment. Additionally, as the species sensitivity between freshwater and marine fish and algae is within a factor of 10, data from fresh and marine water have been pooled to derive the PNEC for the aquatic (freshwater) compartment.
The most sensitive endpoint is the NOEC value based on geometric mean measured concentration from growth inhibition test performed by Dow Chemical on marine algae, *Skeletonema costatum*.
Hence, **the PNEC $_{\text{fresh surface water}}$ is estimated to be 0.049 µg a.i./L** since a safety factor of 10 according to the TGD should be applied to the lowest endpoint for aquatic environment when chronic data for three trophic levels are available. For marine water, an assessment factor of 50 has been applied as no additional chronic data on marine taxonomic group were provided and as acute data on molluscs indicate that algae are the

most sensitive species. **The $PNEC_{marine\ water}$ is therefore estimated to be 0.0098 µg a.i./L.**

For **MIT**, the $PNEC_{fresh\ surface\ water}$ is estimated to be **3.9 µg/L**; based on E_rC_{10} value of 0.039 mg/L (geometric mean from two studies on marine algae, *Skeletonema costatum*) divided by an assessment factor of 10.

Inhibition of aquatic microbial activity

In order to prevent adverse effects of C(M)IT/MIT on microbial activity in STPs, a $PNEC_{microorganisms}$ is derived from the respiration inhibition test according to the OECD guideline 209. The NOEC obtained (0.91 mg a.i./L) divided by an assessment factor of 10 lead to a $PNEC_{microorganisms}$ of 0.091 mg/L.

Whereas the lowest EC50 (4.5 mg a.i./L) divided by an assessment factor of 100 leads to a lower **$PNEC_{microorganisms}$** of **0.045 mg/L**. During the WGI2014, it was discussed if, in this case, the lowest PNEC should be selected for the risk assessment. No clear agreement could have been obtained and it was decided to choose the lowest PNEC as the most conservative approach, expecting further discussions on the interpretation of the TGD**.**

The $PNEC_{microorganisms}$ for MIT is considered (issued from MIT dossier) to be $PNEC_{microorganisms}$ = 0.23 mg/L, **issued from an EC_{50} of 2.3 mg/L (growth inhibition test with *Pseudomonas putida*, ISO 10712) and an assessment factor of 10.**

Sediment dwelling organisms

The study considered relevant for the risk assessment has been conducted by Dow Chemical with *Lumbriculus variegates* exposed to C(M)IT/MIT spiked sediment and provides a NOEC (28d, survival, initial) of 1.93 mg/kg (equivalent to 0.27 mg a.i./kg) dry weight sediment. A safety factor of 10 is applied, resulting in a **$PNEC_{sediment}$** of 0.027 mg a.i./$kg_{dry\ sediment}$ corresponding to **0.0058 mg a.i./$kg_{wet\ sediment}$**.

2.2.2.2.2 Atmosphere

No risks are expected due to high degradability and low volatility of C(M)IT/MIT. Additionally, C(M)IT and MIT are not listed on Annex I of Directive 1005/2009 and are therefore not considered to be ozone depleting substances.

2.2.2.2.3 Terrestrial compartment

For the terrestrial compartment, NOEC values from long-term toxicity tests (on soil microorganisms) are available. A NOEC has been derived from the plant study however, as, acutely, plants are the most sensitive species therefore this study could not be considered as chronic according to MOTA v6. Therefore, an assessment factor of 100 is applied to the lowest NOEC, which was the result of respiration test (28d) on microorganisms (NOEC = 1 mg a.i./kg_{dw}, initial) lead to a **$PNEC_{soil,\ initial}$** of 0.01 mg a.i./$kg_{drysoil}$ corresponding to **0.009 mg a.i./$kg_{wet\ soil}$**. As stated at the 32nd Competent Authority meeting, as degradation half-life is < 2 days, for the risk assessment the initial PNEC is compared to the initial PEC calculated without taking into account any

degradation. Nevertheless, for intended uses leading to continuous release to the soil, PNEC twa has been calculated to be 0.0004 mg a.i./$kg_{wet\ soil}$ taking into account of a half life in soil of 0.78 d at 20°C.

For release through the spreading of STP sludge, the initial $PNEC_{soil}$ for MIT is considered to be **PNEC soil = 0.0417 mg a.i./$kg_{wet\ soil}$** from EC_{50} of 18 mg a.i./$kg_{dry\ soil}$ issued from a plant tests and an assessment factor of 1000 (issued from MIT dossier).

2.2.2.2.4 Summary of PNEC values

Table 2.2.2-1: Summary of the selected PNEC values used for the risk characterisation part

ENVIRONMENTAL COMPARTMENT	PNEC		Unit
	C(M)IT/MIT	MIT	
$PNEC_{fresh\ surface\ water}$	0.049	3.9	µg a.i./L
$PNEC_{marine\ water}$	0.0098	-	µg a.i./L
$PNEC_{stp}$	0.045	0.23	mg a.i./L
$PNEC_{soil,\ initial}$	0.009	0.0417	mg a.i./kg_{wwt}
$PNEC_{soil,\ TWA}$	0.0004	-	mg a.i./kg_{wwt}

2.2.2.3 Environmental effect assessment (product)

No additional data on the environmental effects of the biocidal products were submitted. The risk assessment is based on the effect of the active substance C(M)IT/MIT.

2.2.2.4 PBT Assessment and endocrine properties

According to the PBT assessment in the Annex XIII from the REACH regulation, substances are classified when they fulfil the criteria for all three inherent properties Persistent, Bioaccumulable, Toxic.

2.2.2.4.1 Persistance criteria

According to the PBT assessment in the Annex XIII from the REACH regulation, criteria for substance to be persistent are fulfilled when:
$T_{1/2}$ in marine water > 60 days or,
$T_{1/2}$ in freshwater > 40days or,
$T_{1/2}$ in marine: sediment > 180 days or,
$T_{1/2}$ in freshwater: sediment > 120 days, or $T_{1/2}$ in soil > 120 days.

In simulation tests, the degradation half-lives of both substances in aerobic estuarine water microcosm and in aerobic water/sediment are less than 6 days (12°C). Considering these data, the active substance C(M)IT/MIT does not fulfilled the P criteria. Relevant metabolites are shown to be either readily biodegradable or transient and are therefore considered to be not persistent.

2.2.2.4.2 B criteria

According to the PBT assessment in the Annex XIII from the REACH regulation, a substance is considered to fulfill the B criterion when the bioconcentration factor (BCF) exceeds a value of 2 000 L/kg.
The potential of bioaccumulation of C(M)IT measured from a study conducted in fish (Bluegill sunfish) according to OECD 305 guideline is considered as very low ≤ 54. Because of the log Kow value for MIT is lower than the log Kow value for C(M)IT, and taken into account the results of the previous study, the bioaccumulation potential for MIT will be minimal.
Considering these data, the active substance C(M)IT/MIT is no selected according to the B criteria.

2.2.2.4.3 T criteria

According to the PBT assessment in the Annex XIII from the REACH regulation, the toxicity criterion is fulfilled when the chronic NOEC for aquatic organism is less than 0.01 mg/L or when the substance is toxic to mammals and classified as Very Toxic or Toxic after oral dosing.
Based on ecotoxicity data on *Skeletonema costatum*, NOErC (48-hour, growth inhibition) = 0.49 µg a.i./L (static, measured concentrations), T criteria is fulfilled.

As only one of these P, B, T criteria is fulfilled, the active substance C(M)IT/MIT is not classified according the PBT assessment.

2.2.2.5 Environmental exposure assessment

The risk characterisation has been carried out for the representative products from the two applicants: Kathon™ 886F (Dow Chemical) and Acticide®14 (Thor). Several metabolites have been identified in simulation studies. However, based on their lack of persistence, low potential for bioaccumulation and their low toxicity, it is concluded that the potential for adverse environmental effects in response to exposures to the C(M)IT/MIT metabolites is considered negligible. Then no risk assessment on metabolites of C(M)IT/MIT has been conducted.
The intended uses for Kathon™ 886F and for Acticide®14 are applications to control the growth of bacteria and fungi in water soluble or emulsifiable metal working fluid (MWF) in sumps during use. A part of the solution in water soluble and emulsifiable MWF is directed to STP. Kathon™ 886F is used at concentrations from 10 to 35 ppm and Acticide®14 at concentration from 14 to 42 ppm in the MWF system.
The STP is the primary compartment of exposure. Secondary compartments considered for the risk assessment were surface water, soil and groundwater.

A tiered approach has been considered as the releases were directed to the STP:

In **Tier I**, considering the STP simulation results based on C(M)IT, showing that no parent compound was detected in the effluent phase or in the sludge, C(M)IT was considered to be totally degraded in the STP and no emission of this compound in the different environmental compartments from the STP was foreseen. The only compound considered at the outlet of the STP was MIT. The fractions of MIT emission directed to water and to sludge from the STP were defined from the simulation tests in aerobic sewage treatment for MIT :

- the fraction of MIT emission directed to water by STP was considered as 0.122,
- the fraction of MIT emission directed to sludge by STP was considered as 0.066.

The Tier I risk assessment has been carried out considering a ratio PEC_{MIT} / $PNEC_{MIT}$.

In **Tier II (only for soil and groundwater compartments),** considering the STP half-life value of 0.04 days derived of the STP simulation study on MIT (A7.1.2.2.2.a/02, Dow Chemical) and in coherence with the MIT dossier, the fraction of MIT emission directed to sludge by the STP was considered as 7.18E-04.
The Tier II risk assessment has been carried out considering a ratio PEC_{MIT} / $PNEC_{MIT}$.

In fact, the fraction of MIT emission directed to sludge in the STP of 0.066 proposed in the Tier I assessment was considered to be a large overestimation considering the low potential of adsorption of MIT (Koc = 7.5 $L.kg^{-1}$). In the simulation study in STP (A7.1.2.2.1.a/02, Dow Chemical), the fraction of 6.6% in the sludge represented the total radioactivity measured in this compartment and not the parent compound only. The default value of the fraction adsorbed onto sludge given by Simple Treat model (Fstp sludge = 0.0718%) seems to be more realistic for the active ingredient MIT.

The use phase of Kathon™ 886F Biocide and Acticide®14 Biocide as preservatives for metal working fluids has been evaluated via exposure analysis based on the specific Emission Scenario Document for PT13[6]. The ESD provides detailed information on the method of determining the emission rate of C(M)IT/MIT to wastewater for both water soluble and emulsifiable metal working fluids (MWF).
To determine the predicted environmental exposure concentrations in water, soil and groundwater compartments, equations from the TGD were used. Emissions to air were derived via EUSES.
According to the TGD, as the log Kow values of both substances (C(M)IT and MIT) are < 3 and the Koc values for both substances are < 500 L/kg, sediment effects assessment is not considered as relevant for this active substance. No sediment risk assessment is needed.

2.2.2.6 Risk characterisation

To carry out a quantitative risk assessment for the environment when Kathon · 886F and Acticide®14 are used as a preservative to control microbial contamination in metal working fluids (PT13), the PEC values were compared to the respective PNEC values for the different compartments, resulting in the following PEC/PNEC ratios. The Table below summarized the PEC/PNEC ratios considering the different approaches.

Table 2.2.2-2: PEC/PNEC values for Kathon™ 886F and Acticide®14 use

	PEC/ PNEC ratio			
	10 ppm Kathon · 886F (Dow Chemical)	14 ppm Acticide®14 (Thor)	35 ppm Kathon · 886F (Dow Chemical)	42 ppm Acticide®14 (Thor)
TIER I				
Water soluble MWF				
Sewage treatment plant	0.005	0.007	0.019	0.022
Surface water	0.031	0.044	0.109	0.131
Sediment	n.r.	n.r.	n.r.	n.r.
Agricultural Soil	0.065	0.092	0.229	0.276
Groundwater	< 0.1 µg/L	< 0.1 µg/L	**> 0.1 µg/L**	**> 0.1 µg/L**
Air	n.r	n.r	n.r	n.r
Emulsifiable MWF				

[6] Harmonization of Environmental Emission Scenarios for biocides used as metalworking fluid preservatives (Product type 13) European Commission DG ENV/RIVM, May 2003.

Sewage treatment plant	0.118	0.165	0.412	0.496
Surface water	0.695	0.972	**2.431**	**2.923**
Sediment	n.r.	n.r.	n.r.	n.r.
Agricultural Soil	**1.456**	**2.038**	**5.084**	**6.115**
Groundwater	**> 0.1 µg/L**	**> 0.1 µg/L**	**> 0.1 µg/L**	**> 0.1 µg/L**
Air	n.r	n.r	n.r	n.r
TIER II				
Water soluble MWF				
Agricultural Soil	0.001	0.001	0.002	0.003
Groundwater	< 0.1 µg/L	< 0.1 µg/L	< 0.1 µg/L	< 0.1 µg/L
Emulsifiable MWF				
Agricultural Soil	0.016	0.022	0.055	0.066
Groundwater	< 0.1 µg/L	< 0.1 µg/L	< 0.1 µg/L	< 0.1 µg/L

n r. = not relevant

2.2.2.6.1 Aquatic compartment

Estimated risks from use of Kathon™ 886F or Acticide®14 as preservatives in water soluble metalworking-fluids and emulsifiable metalworking fluids are considered as acceptable for the aquatic organisms, except at maximal doses rates (35 and 42 ppm) for emulsifiable MWF. For the highest intended doses used in emulsifiable metal working fluid, the assessment should be revised at product authorisation level in the light of the new guidance for PT 13 currently under preparation. Acceptable risks for all the dose rates will probably be reached with this new guidance which will propose more realistic parameters for the environmental assessment of this type of product.

2.2.2.6.2 Sewage treatment plant

Estimated risks from the use of Kathon™ 886F or Acticide®14 as preservatives in water soluble metalworking-fluids are considered as acceptable for microorganisms in the sewage treatment plant whatever the dose rates.

2.2.2.6.3 Atmosphere

No risks are expected due to extremely low volatility of C(M)IT/MIT.

2.2.2.6.4 Terrestrial compartment (agricultural soil)

In Tier 1 approach, considering the release of the substance onto the agricultural soil via the application of STP sludge, the risk can be considered as acceptable for a use of Kathon™ 886F or Acticide®14 as preservatives only in water soluble metalworking fluids whatever the dose rates.
In Tier 2 approach, the risk can be considered as acceptable for a use of Kathon™ 886F or Acticide®14 as preservatives in water soluble and emulsifiable metalworking fluids whatever the dose rates.

2.2.2.6.5 Groundwater

In Tier 1 approach, the concentration in porewater under agricultural soil (surrogate for groundwater) is < 0.1 µg/L set up directive 98/83/EC only for a use of Kathon™ 886F or

Acticide®14 as preservative in water soluble working fluids at the dose rates of 10 and 14°ppm.
In a Tier 2 approach, the concentrations in porewater under agricultural soil (surrogate for groundwater) are < 0.1 µg/L set up for pesticides for both uses, in water soluble and emulsifiable working fluids, whatever the dose rates.

These values indicates acceptable risk to groundwater due to the use of C(M)IT/MIT as preservative in water soluble and emulsifiable working fluids at the intended dose rates.

2.2.2.7 Non compartment specific effects relevant to the food chain (secondary poisoning)

Since C(M)IT and MIT have log Kow values less than 3 (0.401 and -0.486, respectively) their potentials for bioaccumulation is considered to be very low. This was confirmed by either measurement or QSAR modelling of the BCF for aquatic and terrestrial organisms.
In addition, toxicokinetic and metabolism studies showed that both C(M)IT and MIT are rapidly excreted and highly metabolized in mammals. This confirms that their potential to accumulate is low and it can be considered that there is no significant risk of secondary poisoning to birds and mammals. In conclusion, the risk of secondary poisoning associated with the use of C(M)IT/MIT to prevent microbial contamination in the process water and conveyor lubrication fluids in food industry applications is considered to be negligible.

2.2.3 Assessment of endocrine disruptor properties

Neither C(M)IT nor MIT are included in the priority list of substances for further evaluation of their role in endocrine disruption established within the Community Strategy for Endocrine Disrupters (COM (1999) 706, COM (2007) 1635).

2.2.4 Overall conclusions

For Human health, since the product is sensitizing, the concentration in the metalworking fluid should not exceed the value of 15 ppm ai.,in order to avoid any effects.

SCENARIO		Human primary exposure		Human secondary exposure		STP	Aquatic compartment	Terrestrial compartment	Groundwater	Air	Secondary poisoning
		Professional	Non professional	Worker	General public						
APPLICATION in metal working fluids											
Continuous dose	**Kathon™ 886F** (Dow Chemical) **< 15 mg ai L^{-1}**	Acceptable*	NR	NR	NR						
	Acticide® 14 (Thor) **< 15 mg ai L^{-1}**	Acceptable*	NR	NR	NR						

*: Considering the wear of PPE and use restricted to trained professionals
NR: Not relevant

SCENARIO		Human primary exposure		Human secondary exposure		STP	Aquatic compartment	Terrestrial compartment	Groundwater	Air	Secondary poisoning
		Professional	Non professional	Worker	General public						
APPLICATION in water soluble metal working fluid											
Continuous dose	**Kathon™ 886F** (Dow Chemical) **10 mg ai L^{-1}**					Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
	Acticide® 14 (Thor) **14 mg ai L^{-1}**					Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
	Kathon™ 886F (Dow Chemical) **35 mg ai L^{-1}**					Acceptable	Acceptable	Acceptable	Acceptable	NR	NR

SCENARIO		Human primary exposure		Human secondary exposure		STP	Aquatic compartment	Terrestrial compartment	Groundwater	Air	Secondary poisoning
		Professional	Non professional	Worker	General public						
	Acticide³14 (Thor) **42 mg ai L^{-1}**					Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
APPLICATION in emulsifiable metal working fluid											
Continuous dose	**Kathon™ 886F** (Dow Chemical) **10 mg ai L^{-1}**					Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
	Acticide³14 (Thor) **14 mg ai L^{-1}**					Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
	Kathon™ 886F (Dow Chemical) **35 mg ai L^{-1}**					Acceptable	**Not acceptable**	Acceptable	Acceptable	NR	NR
	Acticide³14 (Thor) **42 mg ai L^{-1}**					Acceptable	**Not acceptable**	Acceptable	Acceptable	NR	NR
Overall conclusions: For water soluble MWF, the risk has been considered as acceptable to all environmental compartments. For emulsifiable MWF, the risk has been considered as acceptable to all environmental compartments except at maximal doses rates for aquatic compartment. For these highest dose, the assessment should be revised at product authorisation level in the light of the new guidance for PT 13 currently under preparation.											

NR: Not relevant

2.2.5 Data requirement for the representative product

- The release of biocides used as metalworking fluids has to be considered by the relevant national authorities when issuing permits for recovery plants.
- Acidity according to CIPAC method MT31and information about compatibility of Acticide 14 with other products which will be used with are lacking and will have to be submitted by Thor at the product authorization stage. Moreover details on the "UV resistant" packaging should be provided by Thor at the product authorisation stage.

2.3 OVERALL CONCLUSIONS

The outcome of the assessment for C(M)IT/MIT in product-type 13 is specified in the BPC opinion following discussions at the 10th meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

Appendix I: Listing of endpoints

Listing of end points to be included in the document Overall Summary and Assessment - Doc. I [7]

Note: The owner of data is marked before or after endpoints where relevant: T = THOR, DOW (previously Rohm & Haas)..
In case of several values in each toxicological endpoints, the value used in risk assessment is indicated in bold. Concerning the environmental risk assessment two values per endpoint are given in most cases.

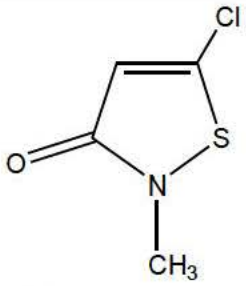
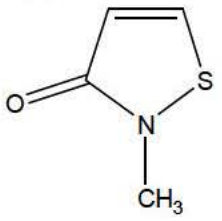
Chapter 1: Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling

Active substance (ISO Common Name)	No ISO name accepted or proposed. The active ingredient common name used is:C(M)IT/MIT (3:1)
Function (*e.g.* fungicide)	Broad spectrum preservative biocide. Bactericide and fungicide.
Rapporteur Member State	France

Identity (Annex IIA, point II.)

Chemical name (IUPAC)	Mixture of 5-chloro-2-methylisothiazol-3(2H)-one and 2-methylisothiazol-3(2H)-one
Chemical name (CA)	Mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one
CAS No	55965-84-9 for the mixture C(M)IT/MIT, 26172-55-4 for C(M)IT (5-chloro-2-methyl-4-isothiazolin-3-one) 2682-20-4 for MIT (2-methyl-4-isothiazolin-3-one)
EC No	There is no EC-N° for the mixture. The EC Nrs for both individual substances are: 247-500-7 for C(M)IT 220-239-6 for MIT.
Other substance No.	No
Minimum purity of the active substance as manufactured (g/kg or g/l)	C(M)IT/MIT (3:1) is manufactured as a TK Min purity of the TC (expressed in dry weight): 57.9% Range of purity of the TK: 139.4-148.5 g/kg of C(M)IT/MIT (3:1), including 105.9-108.8 g/kg of C(M)IT and 33.5-39.7 g/kg of MIT (DOW)

[7] Other end points will be relevant in particular cases - decisions as to the additional end points to be included can only be made on a case by case basis.

	122.1-157.8 g/kg of C(M)IT/MIT (3:1), including 94.7-116.6 g/kg of C(M)IT and 27.4-41.2 g/kg of MIT (DOW) 258.9-300.7 g/kg of C(M)IT/MIT (3:1), including 193.2-228.5 g/kg of C(M)IT and 65.7-72.2 g/kg of MIT (DOW) 138-144 g/kg of C(M)IT/MIT (3:1), including 104-107 g/kg of C(M)IT and 34-37 g/kg of MIT (T)
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Magnesium chloride and magnesium nitrate
Molecular formula	C_4H_4ClNOS for C(M)IT C_4H_5NOS for MIT
Molecular mass	149.6 g/mol for C(M)IT 115.2 g/mol for MIT
Structural formula	 C(M)IT  MIT

Physical and chemical properties (Annex IIA, point III., unless otherwise indicated)

Melting point (state purity)	<u>C(M)IT</u>: melting onset at 51.3°C, with a peak at 54.9°C (purity = 99.86%) (DOW) 46.6-48.9°C (purified) (Thor) <u>MIT:</u> 46.7-48.3°C (purity = 99.7%) (DOW) 44.2-47.7°C (purity = about 100%) (Thor) <u>C(M)IT/MIT (3:1)</u>: melting onset at 22.2°C, with a peak at 35.1°C (purity = 98.7 %) (DOW) < -25 °C (concentration = 14.05 % in water) (DOW)

	-23°C (concentration not stated, ~14% C(M)IT/MIT in water) (Thor)
Boiling point (state purity)	C(M)IT: no boiling point observed until decomposition (purity > 98%) (Thor) MIT: no boiling point observed until decomposition (purity > 99%) (Thor) C(M)IT/MIT (3:1): boiling did not occur until decomposition at 97.3°C (purity = 98.7%) (DOW) 100.1 ± 0.2°C (concentration = 13.7-13.8 % in water) (DOW) 106.5°C (concentration not stated, ~14% in water) (Thor)
Temperature of decomposition	C(M)IT: above 167°C (purity > 98%) (Thor) MIT: above 236°C (purity > 99%) (Thor) C(M)IT/MIT (3:1): 97.3°C (purity = 98.7%) (DOW)
Appearance (state purity)	C(M)IT/MIT (3:1): Solid, pale yellow to yellow at 20 °C, weakly sweet and pungent (purity = 97.8-99.3 %) (DOW) Clear liquid pale yellow at 20°C (concentration = 14.05 % in water) (DOW) Liquid, colorless to pale yellow, mild odor (concentration not stated, ~14% C(M)IT/MIT in water) (Thor)
Relative density (state purity)	C(M)IT: 1.6g/cm^3 at 20.8°C (purity > 98%) (Thor) MIT: 1.39g/cm^3 at 20°C (purity > 99%) (Thor) C(M)IT/MIT (3:1): 1.396 g/cm^3 at 38°C (molten phase), 1.420 g/cm^3 at 25°C (solid phase) (purity = 98.7 %) (DOW) 1.296 g/mL at 25ºC (concentration = 13.7-13.8 % in water) (DOW) 1.256g/ml at 20°C (concentration not stated, ~14% C(M)IT/MIT in water) (Thor)
Surface tension	C(M)IT/MIT (3:1): 72.3 mN/m at 20.0ºC (1g/L C(M)IT/MIT 3:1) (DOW) 73.0 mN/m at 19.5ºC (1g/L C(M)IT/MIT 3:1) (DOW) 72.6mN/m (concentration 1.106g/L) (Thor)
Vapour pressure (in Pa, state temperature)	C(M)IT: 0.9Pa at 20°C and 1.3Pa at 25°C (purity = 99.86%) (DOW) 1.6Pa at 20°C (extrapolated) and 2.8Pa at 25°C(measured) (purity = 98.4%) (Thor) MIT: 2.1Pa at 33°C, measured ; 0.4Pa at 20°C and 0.7 Pa at 25°C, extrapolated (purity = 99.7%) (DOW)

	0.99Pa at 20°C and 1.6Pa at 25°C (extrapolated) (purity = 98.5%) (Thor) C(M)IT/MIT (3:1): 2.2Pa at 20°C and 3.8Pa at 25°C, extrapolated (purity = 98.7%) (DOW) 2080Pa at 20°C, actually the vapor pressure of water (concentration not stated, ~14% C(M)IT/MIT in water) (Thor)
Henry's law constant (Pa m^3 mol^{-1})	C(M)IT: k< 4.26×10^{-4} Pa m^3 mol^{-1} at 20°C and k< 7.07×10^{-4} Pa m^3 mol^{-1} at 25°C (purity = 98.4%) (Thor) MIT: k< 2.72×10^{-5} Pa m^3 mol^{-1} at 20°C and k< $4.39.10^{-5}$ Pa m^3 mol^{-1} at 25°C (purity = 98.5%) (Thor) C(M)IT/MIT (3:1): k< 10^{-4} $Pa.m^3.mol^{-1}$ at 20°C (estimated) (purity = 98.7%) (DOW)
Solubility in water (g/l or mg/l, state temperature)	C(M)IT and MIT (separately tested): extremely soluble in water: 1g of C(M)IT and 4g of MIT are completely dissolved in 1mL of water (respectively 100% and 400% w/v solutions). Solubility not depending on temperature and pH. (Thor) C(M)IT/MIT (3:1): It was not possible to achieve full saturation at nominally 3g/mL. The test sample is therefore of very high solubility (>3000g/l). There is not a significant effect on solubility on increasing the pH from 5 to 9 or increasing the temperature from 9.3 to 20.4□C. The pH of the solution was below 3, even if buffered solutions were used. (purity = 98.7%) (DOW)
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	C(M)IT: (Thor) n-heptane: 14.5g/L xylene: 393g/L Acetonitrile: 1g in 1mL at 10°C and 3.8g in 1mL at 30°C MIT: (Thor) n-heptane: 1.46g/L xylene: 143.6g/L Acetonitrile: 1.4g in 1mL at 10°C and 7.2g in 1mL at 30°C C(M)IT/MIT (3:1): (purity = 95.78-95.51%) (DOW) At 25°C: n-Hexane: 22.5 g/L Ethyl acetate: >763 g/L (not saturated)
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not applicable; biocidal products do not include organic solvents. (DOW and T)
Partition coefficient (log P_{OW}) (state	Measured on active ingredients individually:

temperature)	(DOW) C(M)IT: 0.401 at 24 °C (purity = 98.1%) MIT: - 0.486 at 24 °C (purity = 97.8%) These values will not vary as a function of pH and/or temperature. (DOW) Measured on C(M)IT/MIT (3:1), 13.9% in water: (Thor) C(M)IT: 0.75 MIT: -0.71 Test item is not considered ionisable. Therefore investigation of the pH effect on the partition coefficient is not necessary. (Thor)
Hydrolytic stability (DT_{50}) (state pH and temperature) (point VII.7.6.2.1)	**DOW:** CMIT, RH-651: pH__5____: > 60 days at 25±0.1°C pH__7____: >60 days at 25±0.1°C pH___9___: 22 days at 25±0.1°C, pH__5____: > 170 days at 12°C pH__7____: >170 days at 12°C pH___9___: 62.24 days at 12°C MIT, RH-573: In pH 5, 7, and 9 buffers (24.1 ± 0.4°C) no significant hydrolysis of MIT was observed as the compound was stable for more than 30 days. **Thor:** pH__4____: > 365 days at 20°C pH__7____: >365 days at 20°C pH___9___: 63.6 days at 20°C,
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	Not applicable, C(M)IT and MIT do not dissociate. (DOW and Thor)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	C(M)IT: (Thor)

Solvent	Wavelength	Molar absorption coefficient (L/mol.cm)
Water	274nm	6600
	223nm	4980
HCl (0.1M)	273nm	7280
	222nm	5510
Methanol	279nm	6540
	218nm	5020

MIT: (Thor)

Solvent	Wavelength	Molar absorption coefficient

		(L/mol.cm)
Water	273nm	7600
	<200nm	Maximum below range
HCl (0.1M)	273nm	7630
	<200nm	Maximum below range
Methanol	277nm	7420
	205nm	2140

C(M)IT/MIT (3:1):

purified: (DOW)

Neutral (pH 5.3): λ_{max} at 273nm, $\in$ =7780; λ_{max} at 220nm, $\in$ =4430

Acid (pH 1.3): λ_{max} at 273nm, $\in$ = 7300; λ_{max} at 218nm, $\in$ = 4320

Basic (pH 8.4): λ_{max} at 276nm, $\in$ = 7080; 200nm, $\in$ > 7080

14% in water: (DOW)

Neutral (pH 7): λ_{max} at 272.7nm, $\in$ =9879; λ_{max} at 207.8nm (due to nitrate anion)

Acid (pH 2): λ_{max} at 272.9 nm, $\in$ = 9567; λ_{max} at 209.9nm (due to nitrate anion)

Basic pH: not applicable; C(M)IT/MIT (3:1) is not stable in alkaline conditions.

Photostability (DT_{50}) (aqueous, sunlight, state pH)
(point VII.7.6.2.2)

DOW:

CMIT, RH-651: DT_{50} = 6.6 days at pH 7 and at 24.8±0.5°C

MIT, RH-573: DT_{50} = 11.1 days at pH 7 and at 24.9±0.8°C

Thor:

CMIT,: DT_{50} = 6.3 days at pH 7 and at 25±1°C

MIT,: DT_{50} = 18.2 days at pH 7 and at 25±1°C

Quantum yield of direct phototransformation in water at Σ > 290 nm (point VII.7.6.2.2)

Not determined.

Flammability

C(M)IT and MIT: Not highly flammable (Thor)

C(M)IT/MIT (3:1):

purified: not highly flammable (DOW)

14% in water: not flammable (DOW)

14% in water: not flammable (Thor)

Explosive properties

C(M)IT and MIT: do not have explosive properties (Thor)

C(M)IT/MIT (3:1):
purified: not explosive (DOW)
14% in water: not explosive (DOW)

Classification proposed by the RMS according to the regulation 1272/2008 for C(M)IT/MIT 14% and C(M)IT/MIT 100%

	C(M)IT/MIT 14%	C(M)IT/MIT 100%
Hazard classes and categories	Acute Tox 4 for acute oral hazard Acute Tox 3 for acute dermal hazard Acute Tox 4 for inhalation hazard Skin Corr. 1B Skin Sens. 1A STOT SE 3 Aquatic acute 1 Aquatic Chronic 1	Acute Tox. 3 for acute oral hazard Acute Tox 2 for acute dermal hazard Acute Tox 2 for acute inhalation hazard Skin Corr. 1B Skin Sens. 1A STOT SE 3 Aquatic acute 1 Aquatic Chronic 1
Hazard statements	H332: Harmful if inhaled H312: Harmful in contact with skin H302: Harmful if swallowed H 314: Causes severe skin burns and eye damage H 317: May cause an allergic skin reaction (H 335: May cause respiratory irritation) H400: Very toxic to aquatic life M-factor=10 H410: Very toxic to aquatic life with long lasting effects M-factor=10	H 330: Fatal if inhaled H 310: Fatal in contact with skin H 301: Toxic if swallowed H 314: Causes severe skin burns and eye damage H 317: May cause an allergic skin reaction (H 335: May cause respiratory irritation) H400: Very toxic to aquatic life M-factor=100 H410: Very toxic to aquatic life with long lasting effects M-factor=100
Specific concentration limit	Skin Corr. 1B; H314: Causes severe skin burns and eye damage C ≥ 0.6%** Eye Irrit. 2; H319: Causes serious eye irritation Skin Irrit. 2; H315: Causes skin irritation 0.06% ≤ C < 0.6% Skin Sens.Cat 1A/H317: May cause an allergic skin reaction C ≥ 0.0015% This specific concentration limit is considered as relevant for this dossier.	

****** A classification as Skin Corr. 1C H 314: Causes severe skin burns and eye damage should be required due to the study results, however a harmonised classification as Skin Corr. 1B has been set, and therefore this classification is retained in the dossier.

Classification proposed by the RMS according to the directive 67/548/EEC for C(M)IT/MIT 14% and C(M)IT/MIT 100%

	C(M)IT/MIT 14%	C(M)IT/MIT 100%
Class of danger	Xn - Harmful C: Corrosive Xi: Irritant	T+ - very Toxic C: Corrosive Xi: Irritant

	N: Dangerous to the environment	N: Dangerous to the environment
R phrases	R20/21/22: Harmful by inhalation, in contact with skin and if swallowed R34: Causes burns. (R37 : Irritating to the respiratory tract) R43: May cause sensitization by skin contact R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.	R26/24/25: Very toxic by inhalation, toxic in contact with skin and if swallowed. R34: Causes burns. (R37 : Irritating to the respiratory tract) R43: May cause sensitization by skin contact. R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
S phrases	S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S28: After contact with skin, wash immediately with plenty of water S36/37/39: Wear suitable protective clothing, gloves and eye/face protection. S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). S60: This material and its container must be disposed of as hazardous waste. S61: Avoid release to the environment. Refer to special instructions/Safety data sheets.	
Specific concentration limit	C, R34: Causes burns C ≥ 0.6% Xi, R36/38: Irritating to eyes and skin 0.06% ≤ C < 0.6% Xi; R43: May cause sensitization by skin contact C ≥ 0.0015% This specific concentration limit is considered as relevant for this dossier.	

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	DOW: Reversed Phase High Performance Liquid Chromatography with UV detection (254 nm) Thor: HPLC-UV (275 nm)
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1)	DOW: Titration and GC-FID Validation data are missing on some impurities and should be provided Thor: Titration and NMR-spectroscopy Validation data are missing on the impurities and should be provided

Analytical methods for residues

Soil (principle of method and LOQ) (Annex IIA, point 4.2)	DOW: Extraction and purification followed by reversed phase HPLC with UV detection (275 nm); LOQ=0.05µg/g of soil or sediment (for both

	C(M)IT and MIT) No confirmatory submitted. No confirmatory method is needed due to the rapid degradation of C(M)IT and MIT in soil. Thor: No method submitted. No method is needed due to the rapid degradation of C(M)IT and MIT in soil
Air (principle of method and LOQ) (Annex IIA, point 4.2)	DOW: Trap airborne C(M)IT and MIT on OVS tube, extract and analyze by HPLC/MS/MS; LOQ=2.6µg/m^3 MIT; 7.5µg/m^3 C(M)IT Thor: GC-MSD, LOQ=0.0025 mg/m3 for C(M)IT and 0.0008 mg/m3 for MIT for 12 L of sampled air
Water (principle of method and LOQ) (Annex IIA, point 4.2)	DOW: Solid phase extraction followed by HPLC/MS/MS; LOQ=0.05 µg/L (for both C(M)IT and MIT) Thor: C(M)IT and MIT are extracted from water with SPE columns, eluted with ethyl acetate/acetone, and quantified using HPLC-MS/MS analysis; LOQ=0.1µg/L (for both C(M)IT and MIT)
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	DOW and T: Not required C(M)IT/MIT is classified toxic based on local effect rather than systemic effects. Moreover C(M)IT/MIT is readily absorbed, extensively metabolised and rapidly excreted. Parent compound is not detected in urine, bile or faeces. C(M)IT/MIT does not bioaccumulate in the mammal. Moreover, none of the metabolites are considered of concern.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	DOW: Simulated foods (acidic water, water + ethanol, olive oil): Liquid extraction and/or dilution extraction followed by HPLC/MS/MS LOQ: MIT 2.5µg/L, C(M)IT 7.5µg/L Thor: No method submitted. Not necessary due to intended uses.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	DOW: Simulated foods (acidic water, water + ethanol, olive oil): Liquid extraction and/or dilution extraction followed by HPLC/MS/MS LOQ: MIT 2.5µg/L, C(M)IT 7.5µg/L Thor: No method submitted. Not necessary due to intended uses.

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals (Annex IIA, point 6.2)

	DOW	THOR
Rate and extent of oral absorption:	**C(M)IT: 49 %** MIT: 78%	C(M)IT: 44-47% MIT: 67-69%.
Rate and extent of dermal absorption:	➔ 50% for aqueous solution below corrosive concentration;	➔ 50% for aqueous solution below corrosive

	➔ 100% for corrosive concentration (> 0.6% the specific concentration limit)	concentration; ➔ 100% for corrosive concentration (> 0.6% the specific concentration limit)
Tissue Distribution study:	4 days after exposure: 4.72% of dosed radioactivity found in tissues (rat) Highest amount of radioactivity in blood	
Potential for accumulation:	After oral administration, no evidence of accumulation in the animal body	After dermal exposure C(M)IT/MIT is largely (> 80%) absorbed. However, a large part remains tightly bound to the skin
Rate and extent of excretion:	Following oral administration, C(M)IT and MIT are both rapidly excreted: - C(M)IT: urine and faeces are equal major routes of excretion whereas bile is a minor (4.74%) - MIT: largely excreted in urine and in a lesser extent in faeces of which the major part came from bile (29.09%) No parent compound in excreta.	All the C(M)IT/MIT is rapidly metabolized after oral absorption: no parent compound is found in the excreta. The first step in metabolism was glutathione conjugation, resulting in four major metabolites for MIT and two major metabolites for C(M)IT. The open literature points to the formation of malonic acid, malonamic acid, *N*-methylmalonamic acid and other small polar organic acids.
Toxicologically significant metabolite	None of the metabolites are considered to be of concern.	None of the metabolites are considered to be of concern.

Acute toxicity (Annex IIA, point 6.1)

	DOW	**THOR**
Rat LD_{50} oral C(M)IT/MIT 14% (values for C(M)IT 100% between brackets)	**457 mg/kg bw (corr. to 64 mg a.i./kg bw)**	472 mg/kg bw (corr. to 66 mg a.i./kg bw)
Rat LD50 oral, N-(methyl) malonamic acid (NMMA)	3550 mg NMMA/kg b.w. in males 4100 mg NMMA/kg b.w. in females	
Rat; Rabbit LD_{50} dermal C(M)IT/MIT 14% (values for C(M)IT 100% between brackets)	**Rabbit = 660 mg/kg bw (corr. to 92.4 mg a.i./kg bw)**	Rat > 1007 mg/kg bw (corr. to 141 mg a.i./kg bw)
Rat LC_{50} inhalation C(M)IT/MIT 14% (values for C(M)IT 100% between brackets)	2.36 mg/L (corr. to 0.33 mg a.i./L)	**1.23 mg/L (corr. to 0.171 mg a.i./L)**

Skin irritation (rabbit) C(M)IT/MIT 14% (and C(M)IT/MIT 100%)	Irritant	**Corrosive**
Eye irritation (rabbit) C(M)IT/MIT 14% (and C(M)IT/MIT 100%)	**Corrosive**	Not tested, but C(M)IT/MIT is considered to pose a risk of serious damage to the eyes
Airway irritation C(M)IT/MIT 14%	RD_{50}= 69µg/L (corr. to 9.66 µg a.i/L)	
Skin sensitization (test method used and result) C(M)IT/MIT 14% (and C(M)IT/MIT 100%)	**Sensitising**	**Sensitising**
N-(Methyl) malonamic acid (NMMA)	Not sensitising	

Repeated dose toxicity (Annex IIA, point 6.3)

C(M)IT/MIT 14% (values in a.i. between brackets for C(M)IT/MIT 100%)

	DOW	**THOR**
Species/ target / critical effect	Rabbit-rat / Irritation at site of administration.	Rabbit-rat-dog / Irritation at site of administration.
Lowest relevant oral NOAEL / LOAEL	Rabbit, 28 days - NOAEL = 27.9 mg/kg bw/ day based on no systemic effects (corr. to 3.9 mg a.i./kg bw/d) - NOAEC = 2.9 mg/kg bw/ day based on the fundus irritation (corr. to 0.4 mg a.i./kg bw/d) **Rat, 90 days** - NOAEL = 116/176 mg/kg bw/d based on no signs of systemic effects (corr. to 16.3/24.7 mg a.i./kg bw/d) (for males / females respectively) **- NOAEC = 536 ppm based on gastric irritation toxic effects (corr. to 75 ppm a.i.)** **Rat, 2 years** -NOAEL = 123/184 mg/kg bw/d (corr. to 17.2/25.7 mg a.i./kg bw/d) (for males/females respectively) **-NOAEC = 210 ppm (corr. to 30 ppm a.i. or 2– 3.1 mg ai/kg**	**Rat, 90 days (Letter of access)** - NOAEL = 116/176 mg/kg bw/d based on no signs of systemic effects (corr. to 16.3/24.7 mg a.i./kg bw/d) (for males / females respectively) **- NOAEC = 536 ppm based on gastric irritation toxic effects (corr. to 75 ppm a.i.)** Dog, 90 days NOEL = 157 mg/kg bw/d (corr. to 22 mg a.i./kg bw/ day) **Rat, 2 years (Letter of access)** -NOAEL = 123/184 mg/kg bw/d (corr. to 17.2/25.7 mg a.i./kg bw/d) (for males/females respectively) **-NOAEC = 210 ppm (corr. to 30 ppm a.i. or 2 – 3.1 mg ai/kg**

	bw/d male and female resp.)	**bw/d male and female resp.)**
Lowest relevant dermal NOAEL / LOAEL	Rabbit, 90 days LO(A)EL = 710 ppm (corr. to 100 ppm a.i. equivalent to 0.7 mg/kg bw/d (corr. to 0.1 mg a.i/kg bw/d) based on systemic and local effects observed at this dose. Mouse, 30 months NOAEL = 2857 ppm (corr. to 400 ppm a.i. corr. to 0.25 mg a.i./kg.bw/d)	**Rat, 90 days** - NOEL = 18.75 mg/kg/d (corr. to 2.61 mg a.ikg bw/day) based on no systemic effects **- NOAEC = 12 500 ppm (corr. to 1740 ppm a.i) based on local effects**
Lowest relevant inhalation NOAEL / LOAEL	**Rat, 90 days** **NOAEC = 2.4 mg/m³ (corr. to 0.34 mg a.i./m³ based on irritation to the respiratory tract)**	**Rat, 90 days (Letter of access)** **NOAEC = 2.4 mg/m³ (corr. to 0.34 mg a.i./m³ based on irritation to the respiratory tract)**

Repeated dose toxicity of C(M)IT/MIT metabolites (Annex IIA, point 6.3)

	DOW	**THOR**
Species/ target / critical effect	Rat/-	
Lowest relevant oral NOAEL / LOAEL	N-methyl malonamic acid (NMMA): 90 days NOEL (diet, rat) = 13-15 mg NMMA/kg bw/day (110-220 ppm), the highest dose tested. Malonamic acid (MA): 90 days NOEL (diet, rat) = 2.6-3.0 mg MA/kg bw/day (22-44 ppm), the highest dose tested.	

Genotoxicity (Annex IIA, point 6.6)	Genotoxic *in vitro* (Ames, mammalian cell gene mutation test) Not a genotoxic *in vivo* (*in vivo* unscheduled DNA synthesis, *in vivo* chromosome aberration assay)	Genotoxic *in vitro* (Ames, mammalian chromosome aberration test, mammalian cell gene mutation test) Not a genotoxic *in vivo* (*in vivo* unscheduled DNA synthesis, *in vivo* bone marrow micronucleus test)

Genotoxicity of C(M)IT/MIT metabolites (Annex IIA, point 6.6)	N-methyl malonamic acid (NMMA): **Not mutagenic** (Bacterial Gene Mutation Assay test)	

Carcinogenicity (Annex IIA, point 6.4)

	DOW	**THOR**
Species/type of tumour	Rat, 2 years, oral drinking water **No evidence of carcinogenicity**: no effects on type or incidence of	Rat, 2 years, oral drinking water (Letter of access) **No evidence of carcinogenicity**:

	neoplasms at up to and including 2140 ppm (corr. to 300 ppm a.i.) equivalent to 17.2 and 25.7 mg a.i./kg bw/d for systemic effects for males and females respectively Mice, 30-months study **No evidence of carcinogenicity**: results of histopathology didn't show any indication of a treatment-related increased incidence of neoplasm of any type was seen either locally (at the application site) or systemically	no effects on type or incidence of neoplasms at up to and including 2140 ppm (corr. to 300 ppm a.i.) equivalent to 17.2 and 25.7 mg a.i./kg bw/d for systemic effects for males and females respectively
lowest dose with tumours	No evidence of carcinogenicity	No evidence of carcinogenicity

Reproductive toxicity (Annex IIA, point 6.8)

For C(M)IT/MIT 14% (values in a.i. between brackets for C(M)IT/MIT 100%)

	DOW	**THOR**
Species/ Reproduction target / critical effect	No effects on reproductive capability in rats.	No effects on reproductive capability in rats.
Lowest relevant reproductive NOAEL / LOAEL	Rat: no effects on fertility/mating, post-natal development (one-generation and two-generation)	Rat: no effects on fertility/mating, post-natal development (one-generation and two-generation)
Species/Developmental target / critical effect	Rat, rabbit: no developmental effects	Rat: no developmental effects
Lowest relevant developmental NOAEL / LOAEL	Rat: NOAEL maternal = 100 mg/kg bw/d (corr. to 15 mg a.i./kg bw/day) **NOAEL developmental = 100 mg/kg/d (corr. to 15 mg a.i./kg bw/day)** Rabbit: NOAEL maternal = 57 mg/kg bw/d (corr. to 8 mg a.i./kg bw/day) based on no systemic effects = NOAEL developmental NOAEC maternal = 14 mg/kg bw/d (corr. to 2 mg a.i./kg/day) based on decreased body weight and food consumption due do gastric irritation	Rat **NOAEL maternal = 28 mg/kg bw/d (corr. to 3.95 mg a.i./kg bw/day)** NOAEL developmental = 139 mg/kg bw/d (corr. to 19.6 mg a.i./kg bw/day) Rabbit (Letter of access): NOAEL maternal = 57 mg/kg bw/d (corr. to 8 mg a.i./kg bw/day) based on no systemic effects = NOAEL developmental NOAEC maternal = 14 mg/kg bw/d (corr. to 2 mg a.i./kg/day) based on decreased body weight and food consumption due do gastric irritation

Neurotoxicity / Delayed neurotoxicity (Annex IIIA, point VI.1)

	DOW	**THOR**
Species/ target/critical effect	No evidence of neurotoxicity in multiple dose studies (rat, rabbit, mouse, dog)	No evidence of neurotoxicity in multiple dose studies (rat, rabbit, mouse, dog)
Lowest relevant	No evidence of neurotoxicity in	No evidence of neurotoxicity in

developmental NOAEL / LOAEL.	multiple dose studies (rat, rabbit, mouse, dog)	multiple dose studies (rat, rabbit, mouse, dog)

Other toxicological studies (Annex IIIA, VI/XI)

.....	none

Medical data (Annex IIA, point 6.9)

.....	Despite some incidents over the years, no worker has experienced any continuing skin problems and none has had to be transferred to other duties due to exposure to chemicals.

Summary (Annex IIA, point 6.10)

AEL (Acceptable Exposure Level (C(M)IT/MIT 3:1)	NO(A)EL	Study	Safety factor
Acute, mid-term AEL= 0.11 mg ai/kg bw/d	22 mg ai/kg bw/d	90-day	100
Long-term AEL= 0.09 mg ai/kg bw/d	17.2 mg ai/kg bw/d	24-month	100
AEC (Acceptable Exposure Concentration (C(M)IT/MIT 3:1)	NOAEC	Study	Safety factor
Oral route:	NR	NR	NR
Dermal route(irritation):	Specific concentration limit for sensitising effect: 15 ppm		
Inhalation route:			
Acute, mid-term $AEC_{inhalation}$ = 0.04 mg a.i./m^3	0.34 mg a.i./m^3	90-day	8
Long-term $AEC_{inhalation}$ = 0.02 mg a.i./m^3	"	"	16
ARfD (acute reference dose) = 0.02 mg a.i/kg bw/d	2 mg ai/kg bw/d	Developmental study in rabbit	100
ADI (Acceptable Daily Intake) = 0.004 mg a.i/kg bw/d	0.4 mg ai/kg bw/d	28-day	100

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water (Annex IIA, point 7.6, IIIA, point XII.2.1, 2.2)

DOW	**THOR**

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	CMIT, pH 5: stable pH 7: stable pH 9 : 16.9 and 22 days at 25 °C (47.8 and 62.2 days at 12°C) MIT, pH 5, 7, and 9 : stable	tested as ACTICIDE® 14 pH 4: MIT and CIT stable pH 7: MIT and CIT stable pH 9: MIT stable pH 9: CIT : 63.6 days at 20°C (120.6 days at 12°C) and 15.8 days at 30°C (66.7 days at 12°C)
	CMIT: pH 4, 5, 7: stable, pH 9 : 62.4-120.6 days at 12°C **MIT: pH 4, 5, 7, 9 : stable** **C(M)IT/MIT : stable to hydrolysis at environmental pH**	
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	CMIT, DT_{50} = 6.6 days at 24.8°C, pH 7 and sunlight	CIT DT_{50} = 6.3 days at 25°C pH 7 and sunlight
	MIT, DT_{50} = 11.1 days at 24.9°C, pH 7 and sunlight	MIT DT_{50} = 18.2 days at 25°C, pH 7 and sunlight
	CMIT DT_{50} = 6.6 days at pH 7 (sunlight) **MIT DT_{50} = 18.2 days at pH 7 (sunlight)** **C(M)IT/MIT: DT_{50} = 18.2 days (endpoint for the risk assessment)**	
Readily biodegradable (yes/no)	CMIT, Readily biodegradable with a failure of the 10 day window MIT, Not readily biodegradable	Tested as ACTICIDE® 14 Not readily biodegradable
	C(M)IT/MIT: not readily biodegradable	
Biodegradation in Sewage Treatment Plant	CMIT, $DT_{50\ (dissipation)}$= 0.27 day at 22°C $DT_{50\ (mineralisation)}$= 0.36 day at 22°C MIT, $DT_{50\ (dissipation)}$= 0.03-0.04 day at 22°C $DT_{50\ (mineralisation)}$= 1.69 days at 22°C	Tested as ACTICIDE® 14 CIT: elimination >96% MIT: elimination >80% Tested on MIT only MIT: $DT_{50\ (dissipation)}$= 0.02 day
	Sewage Treatment Plant **CMIT DT_{50} = 0.27 day at 22°C** **MIT DT_{50} = 0.04 day at 22°C**	
Biodegradation in Sewage Treatment Plant (metabolites)	Not relevant	No relevant
Biodegradation in surface water	Estuarine water CMIT, DT_{50} = 0.81 (22 µg/L) -3.17 days	Estuarine water Not available

	(115 µg/L) at 19.6 °C DT_{50} = 1.49 (22 µg/L) – 5.82 days (115 µg/L) at 12 °C MIT, DT_{50} = 1.38 (22 µg/L) -1.24 days (112 µg/L) at 20 °C DT_{50} = 2.63 (22 µg/L) – 2.35 days (112 µg/L) at 12 °C Marine water CMIT, DT_{50} = 1.8 (10 µg/L) – 17.3 days (100 µg/L) at 20°C DT_{50} = 3.4 (10 µg/L) – 32.8 days (100 µg/L) at 12 °C DT_{50} = 4.3 (10 µg/L) – 41.7 days (100 µg/L) at 9 °C MIT, DT_{50} = 3.6 for threshold and 8.3 for PEC calculation (10 µg/L) – 12.3 days (100 µg/L) at 20°C DT_{50} = 6.8 for threshold and 15.7 for PEC calculation (10 µg/L) – 23.3 days (100 µg/L) at 12 °C DT_{50} = 8.7 for threshold and 20.0 for PEC calculation (10 µg/L) – 29.7 days (100 µg/L) at 9 °C	Marine water CIT (20µg/L): DT_{50} = >2 days and < 7 days at 15°C DT_{50}>2.5 and < 8.9 days at 12°C DT_{50} > 3.2 and <11.3 days at 9°C MIT (87.5 µg/L): DT_{50} = 3.9 days at 15°C DT_{50} = 5.0 days at 12°C DT_{50} = 6.3 days at 9°C
	Estuarine water **CMIT DT_{50} = 5.82 days at 12°C** **MIT DT_{50} = 2.63 days at 12°C** **C(M)IT/MIT: DT_{50} = 5.82 days at 12°C (endpoint for the risk assessment)**	
	Marine water **CMIT DT_{50} = 41.7 days at 9 °C** **MIT DT_{50} = 29.7 days at 9 °C** **C(M)IT/MIT: DT_{50} = 41.7 days at 9 °C (endpoint for the risk assessment if necessary)**	
Distribution in water sediment systems	CMIT, Aerobic conditions: $DT_{50\ whole\ system}$ = 0.38-1.33 days at 20°C $DT_{50\ whole\ system}$ = 0.72-2.47 days at 12°C MIT,	CIT: Aerobic conditions: $DT_{50\ whole\ system}$ = 1.86-2.04 days at 20°C $DT_{50\ whole\ system}$ = 3.53-3.86 days at 12°C MIT: Aerobic conditions:

	Aerobic conditions: $DT_{50\ whole\ system}$ = 0.46-1.44 days at 20°C $DT_{50\ whole\ system}$ = 0.87-2.7 day at 12°C	$DT_{50\ whole\ system}$ = 1.28-2.2 days at 20°C $DT_{50\ whole\ system}$ = 2.43-4.17 days at 12°C
	<u>Aerobic Freshwater/sediment</u> **<u>CMIT</u> DT_{50} whole system = 2.22 days at 12°C (geometric mean)** **<u>MIT</u> DT_{50} whole system = 2.21 days at 12°C (geometric mean)**	
Distribution in water sediment systems (metabolites)	<u>Aerobic, CMIT</u> Not relevant <u>Aerobic, MIT</u> <1% of applied radioactivity except for 2-(methylcarbamoyl)ethane sulfonic acid and 2-hydroxyethane sulfonic acid. maximum 23.5% in Almhouse water:sediment system (0.9 at day 30) and maximum 20.5% in the Cedar Hill water: sediment system, (3.3% at day 30).	<u>Aerobic, CMIT</u> Only detected in the water sediment system with high organic carbon - a polar degradation product (10.1% of applied activity by day 6, 4.6% by day 58) - a degradation product of polarity similar to C(M)IT (13.6% of applied activity by day 13, 3.0% by day 58). Their identity was not elucidated, despite efforts with LC/MS analysis <u>Aerobic, MIT</u> One metabolite detected but not identified in both water:sediment system: - low organic matter water: sediment system, maximum 48.5% by day 4 and 11.4% by day 38 - high organic matter water: sediment system, maximum 36.9% by day 8 and not detected by day 58.
Non-extractable residues	<u>C(M)IT, aerobic</u>: 45.4-69.5 % of the applied ^{14}C-activity with 60.4 % at study termination (30 days) and 34.6-44.4 % with 42.2 % at study termination (30 days) for the Almhouse and Cedar Hill water:sediment systems, respectively). <u>MIT, aerobic</u>: 45.2-60.2 % of the applied ^{14}C-activity with 57.7 % at study termination (30 days) and 27.2-62.6 % with 62.6 % at study termination (30 days) for the Almhouse and Cedar Hill water:sediment systems,	<u>C(M)IT, aerobic</u>: - low organic matter water: sediment system, from 17.0% of applied activity by day 1 to 43.9% by day 58 - high organic matter water: sediment system, from 17.8% of applied activity by day 1 to 51.4% by day 31.5 <u>MIT, aerobic</u>: - low organic matter water: sediment system, from 12.6% of applied activity by day 1 to 53.7% by day 38 - high organic matter water: sediment system, from 15.8% of applied activity by day 1 to

respectively).	42.0% by day 39

Route and rate of degradation in soil (Annex IIIA, point VII.4, XII.1.1, XII.1.4; Annex VI, para. 85)

	DOW	THOR
Mineralization (aerobic)	CMIT, CO_2 was present at 75% of the applied activity after 100 days of incubation.	CIT Not available
	MIT, CO_2 was present at 46.6% of the applied activity after 100 days of incubation.	MIT 25.2% mineralisation after 51 days
Laboratory studies (range or median, with number of measurements, with regression coefficient)	CMIT, DT_{50} = 0.11 day for threshold and 0.78 day for PEC calculation at 20°C DT_{50} = 0.21 day for threshold and 1.48 days for PEC calculation at 12°C	CIT Not available.
	MIT, DT_{50} = 0.27 day at 20°C $DT_{50\ (0\text{-}48h)}$ = 0.51 day at 12°C	MIT DT_{50} < 0.08 day at 20°C DT_{50} < 0.15 day at 12°C
	CMIT DT_{50} = 1.48 days at 12°C **MIT DT_{50} = 0.51 days at 12°C** **C(M)IT/MIT: DT_{50} = 1.48 days at 12°C (endpoint for the risk assessment, PEC calculations)**	
Field studies (state location, range or median with number of measurements)	DT_{50f}: not available	DT_{50f}: not available
	DT_{90f}: not available	DT_{90f}: not available
Anaerobic degradation	Not available	Not available
Soil photolysis	Not available	Not available
Non-extractable residues	CMIT, *Non extractable residues:* from 1.62 % to 76.49 % after 48 hours 58.70% after 64 days	CIT Not available MIT from approximately 33% of the applied activity at t=2h to

	MIT, *Non extractable residues:* from 6.2 % to 39.7 % after 30 days and 38.8 % after 100 days.	approximately 55% of the applied activity at the end of the incubation
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	CMIT, CO_2 was the only metabolite detected and identified that was greater than 10% of the applied radioactivity. The presence of $^{14}CO_2$ demonstrates that the isothiazolone ring is cleaved and significant metabolism of the resulting alkyl metabolites has occurred. While definitive identification of the metabolites could not be achieved, they can be characterized as a mixture of malonic acid, malonamic acid, N-methyl malonamic acid, and N-methyl oxamic acid. MIT, Besides CO_2 , two metabolites were quantified above 10% but were transient. They were isolated and identified by LC-MS as N-methyl-2-oxo-propionamide, and 2-methylcarbamoyl-ethene sulfonic acid. CO_2 increased continually throughout the study reaching 46.6% after 100 days of incubation.	Not applicable (all compounds <10% of the applied activity)
Soil accumulation and plateau concentration	Based on degradation studies, no accumulation is expected.	Based on degradation studies, no accumulation is expected.

Adsorption/desorption (Annex IIA, point XII.7.7; Annex IIIA, point XII.1.2)

	DOW	**THOR**
Ka , Kd	CMIT, Kf (sludge) = 55.6 Ka_{oc} (sludge) = 79.9-107.1 Ka_{oc} (soil and sediment) = 30-310 Kd_{oc} (soil and sediment) = 39-421 MIT, Kf (sludge) = 6.12 Ka_{oc} (sludge) = 54.1-152.7 Ka_{oc} (soil and sediment) = 6.4-10 Kd_{oc} (soil and sediment) not determined	CIT, Ka_{oc} = 11.75 CIT (OECD 106): Ka_{oc} (soil and sediment) = 26-69 MIT Ka_{oc} << 5.6
Ka_{oc} , Kd_{oc}		

pH dependence (yes / no) (if yes type of dependence)	Not expected.	
	CMIT Ka_{oc} (soil and sediment) = 26-310 ; Ka_{oc} (arithmetic mean) = 83.2 **MIT Ka_{oc} (soil and sediment) = 6.4-10; Ka_{oc} (arithmetic mean) = 7.5**	

Fate and behaviour in air (Annex IIIA, point VII.3, VII.5)

	DOW	THOR
Direct photolysis in air	The phototransformation half-lifes in air calculated with OH radicals are 16.4 and 16.6 hours for CMIT and MIT, respectively. For the observed metabolites and degradates of CMIT and MIT the half-lives range from 24.2 to 31.8 hours. The phototransformation half-lifes in air calculated with NO_3 radicals are 29 and 29.9 hours for CMIT and MIT, respectively	The calculated phototransformation half-lifes in air with OH radicals are 17.5 and 14.3 hours for CMIT and MIT, respectively. The calculated phototransformation half-lifes in with ozone air are 45.8 days and 6.55 days for CMIT and MIT, respectively.
	<u>CMIT</u> DT_{50} = 17.5 hours **<u>MIT</u> DT_{50} = 16.6 hours** **<u>C(M)IT/MIT</u>: DT_{50} = 17.5 hours**	
Quantum yield of direct photolysis	Not available	
Photo-oxidative degradation in air	Not available	
Volatilization	Low potential due to low vapour pressure.	

Monitoring data, if available (Annex VI, para. 44)

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	Not available
Ground water (indicate location and type of study)	Not available
A.i.r (indicate location and type of study)	Not available

Chapter 5: Effects on Non-target Species

Toxicity data of C(M)IT/MIT for aquatic species (most sensitive species of each group)
(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Time-scale	**DOW**	**THOR**
		Endpoint	Endpoint
Freshwater Fish			
Rainbow trout (*Oncorhynchus mykiss*)	Acute-96 hr US-EPA 72-1 Flow through	96 hr LC_{50} 1.36 mg/L (eq. to 0.19 mg a.i./L) 96 hr NOEC 0.93 mg /L (eq. to 0.13 mg ai/L) (mean measured concentration)	
	Acute-96 hr OECD 203 Static		96 hr LC_{50} 1.57 mg /L (eq. to 0.22 mg ai/L) (nominal concentration)
Bluegill sunfish (*Lepomis macrochirus*)	Acute-96 hr US-EPA 72-1 Flow through	96 hr LC_{50} 2.00 mg /L (eq. to 0.28 mg ai/L) 96 hr NOEC 1.57 mg /L (eq. to 0.22 mg ai/L) (mean measured concentration)	
Rainbow trout (*Oncorhynchus mykiss*)	Prolonged Toxicity Test -14 Day OECD 204 Flow through	14 d NOEC 0.36 mg /L (eq. to 0.05 mg ai/L) (mean measured concentration)	
	Mortality test -28 Days OECD 215 Semi Static		28d NOEC 0.70 mg /L (eq. to 0.098 mg ai/L) (nominal concentration)
Fathead minnow (*Pimephales promelas*)	Early life stage toxicity-36 days US-EPA 72-4 Flow through	NOEC, egg hatch, survival, length 0.86 mg /L (eq. to 0.12 mg ai/L) NOEC, weight 0.14 mg /L (eq. to 0.02 mg ai/L) (mean measured concentration)	
Saltwater Fish			

Sheepshead minnow (*Cyprinodon variegatus*)	Acute-96 hr Static	96 hr LC_{50} 2.14 mg ./L (eq. to 0.30 mg ai/L) 96 hr NOEC 1.29 mg /L (eq. to 0.18 mg ai/L) (nominal concentration)	
	Acute-96 hr Flow through		96 hr LC_{50} 3.43 mg /L (eq. to 0.48 mg ai/L) (nominal concentration)
Freshwater Invertebrates			
Daphnia magna	Acute-48 hr US-EPA 72-2 Flow through	48 hr EC_{50} 1.14 mg /L (eq. to 0.16 mg ai/L) 48 hr NOEC 0.86 mg ./L (eq. to 0.12 mg ai/L) (mean measured concentration)	
	Acute-48 hr OECD 202 Static		48 hr LC_{50} 4.71 mg ./L (eq. to 0.71 mg/L C(M)IT /MIT 14% a.i. and 0.10 mg ai/L, issued from 2.1% source) (nominal concentration)
Daphnia magna	Chronic-21 days US-EPA 72-4	NOEC, survival of first generation[1], 0.71 mg ./L (eq. to 0.10 mg ai/L) EC_{50}, survival of first generation[1], > 1.29 mg ./L (eq. to 0.18 mg ai/L) (mean measured concentration)	
	Chronic-21 days OECD 202		NOEC reproduction 0.172 mg./L (eq. to 0.026 mg/L C(M)IT /MIT 14% a.i. and 0.0036 mg ai/L, issued from 2.1% source) (mean measured concentration)

[1]: most sensitive parameter

Saltwater Invertebrates

Mysid (*Americamysis bahia*)	Acute-96 hr US-EPA OPPTS 850.1035 Flow through	96 hr EC_{50} 2.01 mg ./L (eq. to 0.282 mg a.i./L) 96 hr NOEC 0.21 mg./L (eq. to 0.030 mg a.i./L) (mean measured concentration)	
	Acute-96 hr US-EPA FIFRA 72-3 Flow through		96 hr EC_{50} 2.36 mg ./L (eq. to 0.33mg ai/L) (nominal concentration)
(Acartia tonsa)	Acute-48 hr ISO TC 147/SC 5 WG 2: and PARCOM Ring Test Protocol Static	48 hr EC_{50} 0.05 mg ./L (eq. to 0.007 mg ai/L) (nominal concentration)	
Crassostrea virginicia (Eastern oyster)	Acute-96 hr US-EPA FIFRA 72-3 Flow through		96 hr LC_{50} 0.29 mg ./L (eq. to 0.041mg ai/L) (nominal concentration)
Freshwater Algae			
Selenastrum capricornutum	120 hr OECD 201 US-EPA FIFRA 122-2 Static	24 hr NOErC 35.3 µg/L (eq. to 4.955 µg ai/L) (Initial measured concentration (LOQ/2))	
	72 hr OECD 201 US-EPA OPPTS 850.5400 Static		72 hr NOErC 8.29 µg ./L (eq. to 1.16 µg ai/L) 72 hr EbC50 69.50 µg /L (eq. to 9.73 µg ai/L) 72 hr ErC50 382.1 µg /L (eq. to 53.5 µg ai/L) (mean measured concentration)
Saltwater Algae			
Skeletonema costatum	48 hr OECD 201 US EPA OPPTS 850.5400 Static	48 hr NOE_rC 3.5 µg/L (eq. to 0.49 µg a.i./L) 48 hr ErC50 37.1 µg/L (eq. to 5.2 µg a.i./L) (mean measured concentration)	Available but no reliable

Freshwater sediment dwelling organisms			
Midge larvae (Chironomus riparius)	Chronic-28 days OECD 218	28 d NOEC, survival 23.79 mg/kg (eq to 3.33 mg a.i./kg) dry sediment 28 d LC_{50}, survival 50.21 mg/kg (eq to 7.03 mg a.i./kg) dry sediment 28 d NOEC, adult emergence 27 mg/kg (eq to 3.78 mg a.i./kg) dry sediment 28 d EC_{50}, adult emergence 50.21 mg/kg (eq to 7.03 mg a.i./kg) dry sediment 28 d NOEC, developmental rate > 50.21 mg/kg (eq to 7.03 mg a.i./kg) dry sediment 28 d EC_{50}, developmental rate > 50.21 mg/kg (eq to 7.03 mg a.i./kg) dry sediment (mean measured concentration)	Not Available
Lumbriculus variegatus	Chronic-28 days Draft OECD	28d EC50 survival 2.64-3.29 mg/kg dry sediment (eq to 0.37 - 0.46 mg a.i./kg dry sediment) 28d NOEC survival 1.93 mg/kg (eq to 0.27 mg a.i./kg) dry sediment (mean measured concentration)	Not Available
Hyalella azteca	Chronic-28 days US-EPA OPPTS 850.1735	28d EC50 survival 13.07-45.39 mg/kg dry sediment (eq to 1.83-6.34 mg a.i./kg dry sediment) 28d NOEC survival 7.93 mg/kg (eq to 1.11 mg a.i./kg) dry sediment (mean measured concentration)	Not Available

Saltwater sediment dwelling organisms - not available			
Microorganisms			
Activated sludge respiration inhibition	Acute-3 hr OECD 209	3 hr NOEC 6.50 mg ./L (eq. to 0.91 mg a.i./L) 3 hr EC_{50} 32.14 mg ./L (eq. to 4.5 mg a.i./L)	3 hr EC_{50} 56.57 mg /L (eq. to 7.92 mg ai/L) 3h EC_{20} 6.93 mg /L (eq. to 0.97 mg a.i./L)

Toxicity data of C(M)IT/MIT metabolites for aquatic species (most sensitive species of each group))
(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Time-scale	**DOW***	
		Endpoint	Toxicity
Freshwater Fish- N-methyl malonamic acid			
Rainbow trout (*Oncorhynchus mykiss*)	Acute-96 hr	96 hr LC_{50} 96 hr NOEC	> 1000 mg /L ≥1000 mg /L (nominal concentration)
Freshwater Fish- N-methyl acetamide			
Rainbow trout (*Oncorhynchus mykiss*)	Acute-96 hr	96 hr LC_{50} 96 hr NOEC	> 694 mg /L ≥ 694 mg /L (mean measured concentration)
Freshwater Fish- Malonamic acid			
Rainbow trout (*Oncorhynchus mykiss*)	Acute-96 hr	96 hr LC_{50} 96 hr NOEC	> 1000 mg /L ≥ 1000 mg /L (nominal concentration)
Freshwater Invertebrates- N-methyl malonamic acid			
Daphnia magna	Acute-48 hr	48 hr EC_{50} 48 hr NOEC	> 986 mg /L ≥986 mg /L (mean measured concentration)
Freshwater Invertebrates- N-methyl-acetamide			
Daphnia magna	Acute-48 hr	48 hr EC_{50} 48 hr NOEC	> 863 mg /L not available (mean measured concentration)
Freshwater Invertebrates- Malonamic acid			
Daphnia magna	Acute-48 hr	48 hr EC_{50} 48 hr NOEC	> 1000 mg /L ≥ 1000 mg /L (nominal concentration)

Freshwater Algae- N-methyl malonamic acid			
Selenastrum Capricornutum	96 hr EC_{50}	96 hr NOEC 96 hr E_bC_{50} 96 hr E_rC_{50}	36 mg /L 58 mg ./L 128 mg /L (nominal concentration)
Freshwater Algae- N-methyl-acetamide			
Selenastrum Capricornutum	96 hr EC_{50}	72 hr NOEC 72 hr E_bC_{50} 72 hr E_rC_{50}	0.51 mg /L 1.6 mg /L 5.8 mg /L (nominal concentration)
Freshwater Algae- Malonamic acid			
Selenastrum Capricornutum	96 hr EC_{50}	96 hr NOEC 96 hr E_bC_{50} 96 hr E_rC_{50}	519 mg /L > 1080 mg /L > 1080 mg /L (initial measured concentration)

***No data provided by THOR**

Effects on earthworms or other soil non-target organisms

	DOW	**THOR**
	OECD 207, 14-days mortality	OECD 207, 14-days mortality
Acute toxicity to Earthworm (*Eisenia foetida*) (Annex IIIA, point XIII.3.2)	- Nominal : LC_{50}(survival)= 618.6 mg /kg dw (eq. to 86.6 mg a.i./kg dw)NOEC(survival)=63.1 mg/kg dw (eq. to 8.83 mg a.i./kg dw) - Twa: LC_{50}(survival)= 49.7 mg /kg dw (eq. to 6.96 mg a.i./kg dw) NOEC(survival)=5.07 mg/kg dw (eq. to 0.71 mg a.i./kg dw)	- Nominal : NOEC (survival) = 180 mg/kg (eq to 26 mg a.i/kg) dw LC_{50} (survival) > 1000 mg/kg (eq to >143 mg a.i/kg) dw - Twa: NOEC (survival) = 14.47 mg/kg (eq to 2.09 mg a.i/kg) dw LC_{50} (survival) > 80.38 mg/kg (eq to >11.49 mg a.i/kg) dw
Reproductive toxicity to Earthworm (*Eisenia foetida)* (Annex IIIA, point XIII.3.2)	Not available	Not available

Effects on soil micro-organisms (Annex IIA, point 7.4)

	DOW	**THOR**
	OECD 216, OECD 217, 28 days	OECD 216, OECD 217, 28 days
Nitrogen mineralization	- Nominal : EC_{50}= 266.4 mg /kg dw (eq. to 37.3	- Nominal : EC_{50} = 214.3 mg / kg d.w (eq.

	mg a.i. /kg dw) NOEC= 71.4 mg /kg dw (eq. to 10 mg a.i. /kg dw) <u>- Twa:</u> EC_{50} = 10.71 mg /kg dw (eq. to 1.50 mg a.i. /kg dw) NOEC = 2.87mg /kg dw (eq. to 0.402 mg a.i. /kg dw)	to 30 mg a.i. /kg dw) NOEC = 114.3 mg / kg dw (eq. to 16 mg a.i /kg dw) <u>- Twa:</u> EC_{50} = 8.14 mg / kg d.w (eq. to 1.14 mg a.i. /kg dw) NOEC = 4.34 mg / kg d.w (eq. to 0.61 mg a.i /kg dw)
Carbon mineralization	EC_{50} = 275.7 mg /kg dw (eq. to 38.6 mg a.i. /kg dw) NOEC = 7.14 mg /kg dw (eq. to 1 mg a.i. /kg dw) <u>- Twa:</u> EC_{50} = 11.08 mg /kg dw (eq. to 1.55 mg a.i. /kg dw) NOEC (nominal) = 0.287 mg /kg dw (eq. to 0.0402 mg a.i. /kg dw)	EC_{50} = 180.71 mg /kg d.w (eq. to 25.3 mg a.i. /kg dw) NOEC = 114.3 mg / kg d.w (eq. to 16 mg a.i /kg dw) <u>- Twa:</u> EC_{50} = 6.87 mg /kg d.w (eq. to 0.96 mg a.i. /kg dw) NOEC = 4.34 mg / kg d.w (eq. to 0.61 mg a.i /kg dw)

Effects on terrestrial vertebrates

	DOW	**THOR**
Acute toxicity to mammals (Annex IIIA, point XIII.3.3)	LD_{50} oral : 457 mg/kg bw (rat) (eq. to 64 mg a.i. /kg bw) LD_{50} dermal : 660 mg./kg bw (rabbit) (eq. to 92.4 mg a.i./kg bw) LC_{50} inhalation : 2.36 mg./L air (rat) (eq. to 0.33 mg a.i./L) Skin irritation : Irritant (rabbit) Eye irritation : Corrosive (rabbit) Skin sensitization : Sensitising	LD_{50} oral : 472 mg/kg bw (rat) (eq. to 64 mg a.i. /kg bw) LD_{50} dermal > 1 007 mg./kg bw (rat) (eq. to 141 mg a.i./kg bw) LC_{50} inhalation : 1.23 mg./L air (rat) (eq. to 0.171 mg a.i./L) Skin irritation : Corrosive (rabbit) Eye irritation : Corrosive (rabbit) Skin sensitization : Sensitising
Acute toxicity to birds (Annex IIIA, point XIII.1.1)	Bobwhite quail : LD_{50} = 460.71 mg /kg bw (eq. to 64.5 mg a.i./kg bw) (nominal concentration)	Not available
Dietary toxicity to birds (Annex IIIA, point XIII.1.2)	Bobwhite quail : LC_0 = 10357 mg /kg (eq. to1450 mg /kg a.i.) in diet. NOEC = 1614 mg /kg (eq. to 226 mg /kg a.i.) based on weight and food consumption LC_{50} = 25257 mg /kg (eq. 3536 mg /kg a.i.) (mean measured concentrations) Mallard Duck: LC_0 = 1614 mg /kg (eq. to 226 mg /kg a.i.) LC_{50} = 6750 mg /kg (eq. to 945 mg /kg a.i.)	Not available

	(mean measured concentrations)	
Reproductive toxicity to birds (Annex IIIA, point XIII.1.3)	Not available	Not available

Effects on honeybees (Annex IIIA, point XIII.3.1)

Acute oral toxicity	Not available
Acute contact toxicity	Not available

Effects on other beneficial arthropods (Annex IIIA, point XIII.3.1)

Acute oral toxicity	Not available
Acute contact toxicity	Not available
Acute toxicity to	Not available

Bioconcentration (Annex IIA, point 7.5)

	DOW	**THOR**
Bioconcentration factor (BCF)	CMIT- Bluegill sunfish: Steady state BCF = 41-54 (total ^{14}C-residues, parent and metabolites) The log P (log octanol:water partition coefficient) for CMIT is 0.401. MIT: not available The log P (log octanol:water partition coefficient) for MIT is -0.486.	EPIWIN: CIT BCF = 3.16 MIT BCF = 3.16
Depuration time (DT_{50}) (DT_{90})	CMIT- Bluegill sunfish: D_{T50} = 0.64-1.6 days MIT: not available	NA
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable	NA

Chapter 6: Other End Points

Effects on Terrestrial plants (Document IIIA, point 7.5)

Terrestrial Plants			**DOW**
Canola, Red Clover, and Rice	OECD 208 21 days Seedling	Canola : - Nominal : EC_{50}, emergence EC_{50}, survival	660 mg /kg dry soil (eq. to 92.4 mg ai/kg)

	emergence and seedling growth Soil incorporation	EC_{50}, shoot weight NOEC, emergence NOEC, survival NOEC, shoot weight <u>- Twa:</u> EC_{50}, emergence EC_{50}, survival EC_{50}, shoot weight NOEC, emergence NOEC, survival NOEC, shoot weight <u>Red Clover</u> : <u>- Nominal</u> : EC_{50}, emergence EC_{50}, survival EC_{50}, shoot weight NOEC, emergence NOEC, survival NOEC, shoot weight <u>- Twa:</u> EC_{50}, emergence EC_{50}, survival EC_{50}, shoot weight NOEC, emergence NOEC, survival NOEC, shoot weight <u>Rice</u> : <u>- Nominal</u> : EC_{50}, emergence EC_{50}, survival EC_{50}, shoot weight NOEC, emergence NOEC, survival NOEC, shoot weight <u>- Twa:</u> EC_{50}, emergence EC_{50}, survival EC_{50}, shoot weight NOEC, emergence NOEC, survival NOEC, shoot weight	218.57 mg /kg dry soil (eq. to 30.6 mg ai/kg) 68.9 mg /kg dry soil (eq. to 9.65 mg ai/kg) 214.3 mg /kg dry soil (eq. to 30 mg ai/kg) 64.3 mg /kg dry soil (eq. to 9.0 mg ai/kg) 19.3 mg /kg dry soil (eq. to 2.7 mg ai/kg) 28.04 mg /kg dry soil (eq. to 3.93 mg ai/kg) 9.29 mg /kg dry soil (eq. to 1.30 mg ai/kg) 2.93 mg /kg dry soil (eq. to 0.41 mg ai/kg) 9.11 mg /kg dry soil (eq. to 1.27 mg ai/kg) 2.73 mg /kg dry soil (eq. to 0.38 mg ai/kg) 0.82 mg /kg dry soil (eq. to 0.11 mg ai/kg) 230.71 mg /kg dry soil (eq. to 32.3 mg ai/kg) 85 mg /kg dry soil (eq. to 11.9 mg ai/kg) 48.36 mg /kg dry soil (eq. to 6.77 mg ai/kg) 64.3 mg /kg dry soil eq. to 9.0 mg ai/kg) 19.3 mg /kg dry soil (eq. to 2.7 mg ai/kg) 19.3 mg /kg dry soil (eq. to 2.7 mg ai/kg) 9.80 mg /kg dry soil (eq. to 1.37 mg ai/kg) 3.61 mg /kg dry soil (eq. to 0.51 mg ai/kg) 2.05 mg /kg dry soil (eq. to 0.29 mg ai/kg) 2.73 mg /kg dry soil eq. to 0.38 mg ai/kg) 0.82 mg /kg dry soil (eq. to 0.11 mg ai/kg) 0.82 mg /kg dry soil (eq. to 0.11 mg ai/kg) > 714.3 mg /kg dry soil (eq. to 100 mg ai/kg dry soil) > 714.3 mg /kg dry soil (eq. to 100 mg ai/kg dry soil) 120 mg /kg dry soil (eq. to 16.8 mg ai/kg) 214.3 mg /kg dry soil (eq. to 30 mg ai/kg) 214.3 mg /kg dry soil (eq. to 30 mg

			ai/kg) 64.3 mg /kg dry soil (eq. to 9.0 mg ai/kg) > 30.35 mg /kg dry soil (eq. to 4.25 mg ai/kg dry soil) > 30.35 mg /kg dry soil (eq. to 4.25 mg ai/kg dry soil) 5.10 mg /kg dry soil (eq. to 0.71 mg ai/kg) 9.11 mg /kg dry soil (eq. to 1.27 mg ai/kg) 9.11 mg /kg dry soil (eq. to 1.27 mg ai/kg) 2.73 mg /kg dry soil (eq. to 0.38 mg ai/kg)
Canola, Red Clover, and Rice	Vegetative vigor Foliar spray	Canola , Red Clover, Rice : NOEC, biomass EC_{50}, biomass	7143 mg /L (eq. to1000 mg a.i./L) > 7143 mg /L (eq. to1000 mg a.i./L)

Appendix II: List of intended uses[8]

Object and/or situation	Member State or Country	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks:
				Type	Conc. of as	method kind	number min max	interval between applications (min)	g as/L min max	water L/m^2 min max	g as/m^2 min max	
Preservation of water-based metalworking fluids prepared from water soluble or emulsifiable concentrates.	FR	C(M)IT/MIT containing biocidal products Kathon ™ 886F (Kathon ™MW)	Bacteria, Fungi	Aqueous concentrate	14% Kathon ™ 886F	Dose directly into the use-dilution tanks of the MWF by manual pouring or using a metering pump to ensure correct dosage and uniform dispersal throughout the system.	Dose as needed (typically every 1-6 weeks) to maintain control of the system.	1-6 weeks depending on the type of application and the results of the fluid monitoring	10 - 35 ppm	N/A	N/A	
PT 13: MWF	FR	ACTICIDE 14	Bacteria, fungi.	SL	14 % C(M)IT/MIT	Automatic dosing device	1-1	2 weeks (max.)	14-42 ppm C(M)IT/MIT	NA	NA	

[8] adapted from: EU (1998a): European Commission: Guidelines and criteria for the preparation of complete dossiers and of summary dossiers for the inclusion of active substances in Annex I of Directive 91/414/EC (Article 5.3 and 8,2). Document 1663/VI/94 Rev 8, 22 April 1998

Appendix III: List of studies

Reference list sorted by section: Dow

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
A2.10/01	Popendorf W., Selim M. S. and Lewis M. Q.	1995	Exposure while applying industrial antimicrobial pesticides. American Industrial Hygiene Association Journal, 56:993-1001.	N	/
A3/01	Petigara, R.B.	2001	Biocides product directives common core data set for active (chemical) substances, Parts 2 and 3: identity, and physical and chemical properties of Kathon™ 886F Biocide. Rohm and Haas Company, Report N° TR-01-058 (December 20, 2001), GLP, Unpublished.	Y(ii)[9]	Rohm and Haas
A3/02	Petigara, R.B.	2003	Biocides product directives common core data set for active (chemical) substances, Parts 2 and 3: identity, and physical and chemical properties of SF-886 Technical. Rohm and Haas company, Report N° GLP-2003-040 (August 12, 2003), GLP, Unpublished.	Y(ii)	Rohm and Haas
A3/03	Derbyshire, R.L.	1990	Product chemistry Kathon™ 886F microbicide, Report N° TR-90-29 (November 26,1990), GLP, Unpublished.	Y(ii)	Rohm and Haas
A3/04	Broughton, H.S.	1993	Characterization of test substance Kathon™ 886F, an MUP, to be used for submission to regulatory agencies in Europe, (December 15, 1993), GLP, Unpublished.	Y(ii)	Rohm and Haas
A3/06	Betteley, J.; Petigara, R.	2001	Kordek™ 573T Industrial Microbicide Physicochemical Properties, (August 13, 2001), GLP, Unpublished.	Y(ii)	Rohm and Haas

[9] Y(ii) : Data protection claimed in accordance with Article 12.1(c) (ii) : Active substance already on the market on 14 May 2000. Data submitted for the first time in support of the first inclusion in Annex I or IA **or** Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA (data generated/submitted after the entry into force of the Directive).

A3/07	Broughton, H.S.	1992	Product chemistry –Series 63: SF-886 Tech Technical grade of active ingredient, (February 19, 1992), GLP, Unpublished.	Y(ii)	Rohm and Haas
A3/08	Padmanaban, A.	2008	High AI Kathon™ 886: Determination of Physico-Chemical Properties – Part 1; International Institute of Biotechnology and Toxicology (IIBAT); Rohm and Haas Company; Report N° GLP-2008-129; GLP / Unpublished	Y(ii)	Rohm and Haas
A3/09	Pandisolvi, S.	2008	High AI Kathon™ 886: Determination of Physico-Chemical Properties – Part 2; International Institute of Biotechnology and Toxicology (IIBAT); Rohm and Haas Company; Report N° GLP-2008-128; GLP / Unpublished	Y(ii)	Rohm and Haas
A3/10	Tremain, S.P.	2008	High A.I. Kathon™ 886: Determination of Hazardous Physico-Chemical Properties; SafePharm Laboratories Ltd.; Rohm and Haas Company; Report N° GLP-2008-133; GLP / Unpublished	Y(ii)	Rohm and Haas
A3/11	Berrios, E.	2008	High AI Kathon 886: Determination of Accelerated Storage Stability; Rohm and Haas Company; Report N° GLP-2008-126; GLP / Unpublished	Y(ii)	Rohm and Haas
A3/12	Berrios, E.	2008	High AI Kathon 886: Determination of Long-Term Storage Stability, three months interim report; Rohm and Haas Company; Report N° GLP-2008-134; GLP / Unpublished	Y(ii)	Rohm and Haas
A4.1.a/01:	Berrios, Efrain	2006	"CIS Dept. Test method #06-111-01, Reverse phase HPLC analysis of Kathon™ 886 Technical for active ingredients" July 20, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.a/02:	Berrios, Efrain	2006	"CIS Dept. Test method #06-111-02, Reverse phase HPLC analysis of Kathon™ 886 Technical for active ingredients" October 3, 2006, Unpublished.	Y(ii)	Rohm and Haas

A4.1.a/03:	Berrios, Efrain	2006	"GLP validation of CIS analytical test method #06-111-01 for the analysis of Kathon™ Tech for active ingredient" under protocol # GLP 24P-2006-106" Rohm and Haas Report # GLP-2006-085, September 12, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/01:	Doshi, Deepak,	2001	"CIS Dept. Test method #89-03-03, Reverse phase HPLC analysis of Kathon™ Formulations for active ingredients" March 5, 2001, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/02:	Doshi, Deepak	2001	"GLP report on validation of CIS test method #89-03-03 (Draft) for the analysis of Kathon™ formulations for active ingredients under protocol # GLP 24P-2000-026" Rohm and Haas Report # GLP-2001-006, February 15, 2001, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/03:	Doshi, Deepak	2003	"Round robin study for the analysis of active ingredients in Kathon™ formulations in support of European Biocidal Product Directives", Rohm and Haas Report # GLP-2002-072, April 1, 2003, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/04:	Eisenschmied, Mark A	2006	"GLP LC-MS peak identity verification of AI in Kathon™ CG and Kathon™ 886F as detected by CIS TM 89-03-03", CAs Technical document # TD2006-182. July 19, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/05:	Eisenschmied, Mark A,	2006	"GLP LC-MS peak identity verification of AI in Kathon™ 39FG as detected by CIS TM 89-03-03", CAS Technical Document # TD2006-096, May 1, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/06 :	Berrios, Efrain	2006	"CIS Dept. Test Method #06-105-01, Reverse phase HPLC analysis of Kathon™ 39FG for active ingredients" May 15, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.b/07:	Berrios, Efrain	2006	"GLP validation of CIS analytical test method #89-03-03 for the analysis of Kathon™ 39FG for active ingredients" Protocol # GLP 24P-2006-027" Rohm and Haas Report # GLP-2006-016, May 15, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.c/01:	Bluder, David	1997	Test Method # 96-53-02,"Ion-pair HPLC method to determine magnesium nitrate in Kathon™ formulations", January 15, 1997, Unpublished.	Y(ii)	Rohm and Haas

A4.1.c/02:	Berrios, Efrain	2006	2006, CIS Dept. Test method #96-53-03, Ion-pair HPLC method to determine magnesium nitrate in Kathon™ formulations" June 15, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.c/03:	Berrios, Efrain	2006	"GLP validation of BRAG analytical test method #96-53-02 for the analysis of Kathon™ 886F for magnesium nitrate", protocol # GLP 24P-2006-083, Rohm and Haas Report # GLP-2006-021, June 08, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.d/01:	Berrios, Efrain	2006	CIS Dept. Test method #06-110-01, "Analysis of Kathon™ 886F for % magnesium chloride using potentiometric titration" June 26, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.d/02:	Berrios, Efrain	2006	CIS Dept. Test method #06-110-02, "Analysis of Kathon™ 886F for % magnesium chloride using potentiometric titration", August 2, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.1.d/03:	Berrios, Efrain	2006	"GLP validation and revision of of CIS analytical test method #06-110-01 for the determination of magnesium chloride in Kathon 886F ", protocol # 24P-2006-097, Rohm and Haas Report # GLP-2006-046, July 25, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.2.a/01:	Marbo, M	2005	Validation of CIS analytic methods to determine RH-886 and RH-573 in soil and sediment Samples. Performed at Rohm and Haas Technical Center, Spring House, PA, USA, Technical Report N°. GLP-2005-009, December 12, 2005, Unpublished.	Y(ii)	Rohm and Haas
A4.2.b/01:	Dr. Krainz Alexander	2006	Test method for the determination of 2-methyl-4-isothiazolin-3-one (RH-573) and 5-chloro-2-methyl-4-isothiazolin-3-one (RH-651) the active ingredients in RH-886 and RH-573 formulations, in air, Test method 857665, June19, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.2.b/02:	Dr. Krainz, Alexander	2006	Development and validation of residue analytical methods for determination of 2-methyl-4-isothiazolin-3-one (RH-573) and 5-chloro-2-methyl-4-isothiazolin-3-one (RH-651) the active ingredients in RH-886 and RH-573 formulations, in air, RCC Ltd., Study # 857665, Rohm and Haas Study # GLP-2005-012, June19, 2006, Unpublished.	Y(ii)	Rohm and Haas

A4.2.c/01:	Dr. Stefan Wolf	2004	Development and validation of a residue analytical method for 5-chloro-2-methyl-4-isothiazolin-3-one (CMIT or RH-651) and 2-methyl-4-isothiazolin-3-one (MIT or RH-573) in Drinking, Surface and Sea Water, RCC Ltd., Study # 852129, Rohm and Haas Report # GLP-2004-042, November 01, 2004, Unpublished.	Y(ii)	Rohm and Haas
A4.2.c/02:	Dr. Stefan Wolf	2004	Test Method for the determination of 5-chloro-2-methyl-4-isothiazolin-3-one (CMIT or RH-651) and 2-methyl-4-isothiazolin-3-one (MIT or RH-573) in Drinking, Surface and Sea Water, RCC Ltd., Study # 852129, Rohm and Haas Report # GLP-2004-042, November 01, 2004, Unpublished.	Y(ii)	Rohm and Haas
A4.3/01:	Dr. Krainz A.	2007	Validation of a residue analytical method for the determination of 2-methyl-4-isothiazoin-3-one (RH-573) and 5-chloro-2-methyl-4-isothiazolin-3-one (RH-651), the active ingredients in Kathon™ 886 in acetic acidic water, water containing ethanol and olive oil (food stimulants), RCC Ltd, Study # B25626, Rohm and Haas Report # GLP-2007-070, August 29, 2007, Unpublished.	Y(ii)	Rohm and Haas
A4.3/02:	Dr. Krainz A.	2007	Test method for the determination of 2-methyl-4-isothiazoin-3-one (RH-573) and 5-chloro-2-methyl-4-isothiazolin-3-one (RH-651), the active ingredients in Kathon™ 886 in acetic acidic water, water containing ethanol and olive oil (food stimulants), RCC Ltd, Study # B25626, August 29, 2007, Unpublished.	Y(ii)	Rohm and Haas
A5.3.1/01	Diehl M A	2005	The Antimicrobial Activity of Chloromethylisothiazolinone + Methylisothiazolinone (CMIT/MIT): "Minimum Inhibitory Concentration (MIC) Studies versus Algae, Fungi, and Bacteria." Rohm and Haas Company, Technical Report Nº TR-05-026 (April 20, 2005), unpublished.	Y(ii)	Rohm and Haas

A5.3.1/02	Diehl M A	2006	Speed of kill (SOK) and multiple challenge efficacy test with Chloromethylisothiazolinone + Methylisothiazolinone (CMIT/MIT) in an in-can model preservative system. Rohm and Haas Company, Technical Report NºBPD-06-017 (May 23, 2006), unpublished.	Y(ii)	Rohm and Haas
A5.4.1/01	Williams T.M	2006	The Antimicrobial Mechanism of Action of Chloromethylisothiazolinone-Methylisothiazolinone (CMIT/MIT) Biocide. Rohm and Haas Company, Technical Report Nº TR-06-064 (July 26, 2006), unpublished.	Y(ii)	Rohm and Haas
A6.1.1/01:	[redacted]	1993	Kathon™ 886 all-magnesium formulation: acute oral toxicity study in male rats, Rohm and Haas Company, Rohm and Haas Report N° 77R-038A, July 23, 1993, Unpublished.	Y(i)[10]	Rohm and Haas
A6.1.1/02:	[redacted]	2006	N-Methyl-malonamic acid acute oral toxicity study in male and female rats (metabolite), Rohm and Haas Company Report N°: 72R-1039 (November 13, 1972 original report; April 13, 2006 additional data), unpublished.	Y(ii)	Rohm and Haas
A6.1.2/01:	[redacted]	1993b	Kathon™ 886 all-magnesium formulation: acute dermal toxicity study in male rabbits, Rohm and Haas Company, Rohm and Haas Report N° 76R-056A, July 23, 1993, unpublished.	Y(i)	Rohm and Haas
A6.1.3.a/01:	[redacted]	1991a	Kathon™ 886F biocide: acute inhalation toxicity study in rats, Rohm and Haas Company, Rohm and Haas Report N° 91R-018, July 10, 1991, Unpublished.	Y(i)	Rohm and Haas
A6.1.3.a/02:	[redacted]	1991b	Kathon™ 886F biocide: acute inhalation toxicity study in rats, Report Supplement, Rohm and Haas Company, Rohm and Haas Report N° 91R-018A, August 12, 1991, Unpublished.	Y(i)	Rohm and Haas
A6.1.3.a/03:	[redacted]	1992	Kathon™ 886F biocide: acute inhalation toxicity study in rats, Report Supplement, Rohm and Haas Company, Rohm and Haas Report N° 91R-018B, June 9, 1992, Unpublished.	Y(i)	Rohm and Haas

[10] Y(i) : Data protection claimed in accordance with Article 12.1(c) (i), as data already submitted in member states before the entry into force of the Directive. Data submitted to the MS before 14 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA.

A6.1.3.b/01:	Papagiannis C.N.	1993	Kathon™ 886F biocide: evaluation of the upper airway irritation potential (RD50), International Research and Development Corporation Project ID: 285-047, Rohm and Haas Report N° 91RC-047, April 23, 1993, Unpublished.	Y(i)	Rohm and Haas
A6.1.4.a/01:	[redacted]	1986	Kathon™ 886 – 13.9 %: determination of the acute dermal irritation or corrosion in male rabbits, [redacted] Protocol N° BT0102, Rohm and Haas Report N° 86RC-1005, November 26, 1986, Unpublished.	Y(ii)	Rohm and Haas
A6.1.4.a/03:	[redacted]	1985	Kathon™ 886 1.5 % Biocide: skin irritation study in rabbits, Rohm and Haas Company, Rohm and Haas Report N° 84R-244A, B, C, D, January 16, 1985, Unpublished.	Y(i)	Rohm and Haas
A6.1.4.b/01:	Longacre, S.L.	1995	Kathon™ 886 Biocide: revised acute toxicity reports, Rohm and Haas Company, Rohm and Haas Report N° 76-56B, March 20, 1995, Unoublished.	Y(i)	Rohm and Haas
A6.1.5/01:	House R.V.	2000a	Murine local lymph node assay with Chloromethylisothiazolinone and Methylisothiazolinone, Covance Laboratories Study ID: 6228-145, Rohm and Haas Report N° 00RC-148A, November 7, 2000, Unpublished.	Y(ii)	Rohm and Haas
A6.1.5/02:	[redacted]	2001	Chloromethylisothiazolinone/Methylisothiazolinone 3:1 - Open epicutaneous test in guinea pigs, [redacted] Project ID N 31H0367/002132, US Ref N° 01RC-1030, July 12, 2001, Unpublished.	Y(ii)	
A6.1.5/03:	House R.V.	2000b	Murine local lymph node assay to evaluate Chloromethylisothiazolinone/Methylisothiazolinone, Covance Laboratories Study ID: 6228-146, Rohm and Haas Report N° 00RC-148B, November 7, 2000, Unpublished.	Y(ii)	Rohm and Haas
A6.1.5/04:	[redacted]	2000	Chloromethylisothiazolinone and Methylisothiazolinone 3:1: Dermal sensitization study in guinea pigs Maximization test, Rohm and Haas Company Report N° 00R-140, September 28, 2000, Unpublished.	Y(i)	Rohm and Haas

A6.1.5/06:	[redacted]	1982	Kathon™ 886: a study of the concentration-dependent delayed contact hypersensitivity in guinea pigs, Rohm and Haas Company, Rohm and Haas Report N° 81R-66, August 24, 1982, Unpublished.	Y(i)	Rohm and Haas
A6.1.5/06bis:	[redacted]	1983	KathonTM Biocide: Manifestation of delayed contact hypersensitivity in guinea pigs is dependent on the concentration for induction and challenge, The Journal of Investigative Dermatology, 81:409-411, 1983, Unpublished, Published.	N	Rohm and Haas
A6.1.5/07:	Chapdelaine J.M.	2003	N-(Methyl) malonamic acid: Local lymph node assay, Calvert Laboratories Report No. 0787XR07.001, Rohm and Haas Report N°: 02RC-049 (August 8, 2003), Unpublished.	Y(ii)	Rohm and Haas
A6.2.a/01:	[redacted]	2005a	Metabolism and pharmacokinetics of 14C-RH-573 in the rat, [redacted] Study N°: XBL01057, Rohm and Haas Report N°: 03RC-043, June 13, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2.a/02:	[redacted]	2005b	Metabolism of 14C-RH-573 in the biliary cannulated rat, [redacted] Report N°: RPT01215, Rohm and Haas Report N°: 04RC-056, July 14, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2.a/03:	[redacted]	2003	Tissue distribution of 14C-RH-573 in the mouse. [redacted], unpublished report, XBL Report N° XBL00994, Rohm and Haas Company Report N° 03RC-042, August 27, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.2.a/04:	[redacted]	2003	2-Methyl-4-isothiazolin-3-one: In vitro percutaneous absorption through rat skin, Rohm and Haas Company, Rohm and Haas Company Report No. 00R-066, August 22, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.2.a/05:	Ward R.J.	2005	2-Methyl-4-isothiazolin-3-one (MI): in vitro absorption from water and three formulations through human epidermis, Central Toxicology Laboratory Study No: JV1839, Rohm and Haas Report N° 04RC-066 (August 16, 2005), Unpublished.	Y(ii)	Rohm and Haas

A6.2.b/01:	[redacted]	2005c	Metabolism of 14C-RH-651 in the rat, [redacted] Study N°: RPT01224, Rohm and Haas Report N°: 04RC-053, August 4, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2.b/02:	[redacted]	2005d	Metabolism of 14C-RH-651 in the biliary cannulated rat, [redacted] Report N°: RPT01229, Rohm and Haas Report N°: 04RC-057, August 4, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2.b/03:	[redacted]	2004	Tissue distribution of 14C-RH-651 in the mouse. [redacted] Inc., unpublished report, XBL Report N° XBL01156, Rohm and Haas Company Report N° 04RC-054, August 31, 2004, Unpublished.	Y(ii)	Rohm and Haas
A6.2.b/04:	Ward RJ	2005	5-Chloro-2-methyl-4-isothiazolin-3-one (CMIT) and 2-Methyl-4-isothiazolin-3-one (MIT) in a 3:1 w/v mixture: in vitro absorption of CMI from aqueous solutions through human epidermis, Central Toxicology Laboratory Study N°: JV1858, Rohm and Haas Report N°: 04RC-067, August 16, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2.b/05:	Ward RJ	2005	5-Chloro-2-methyl-4-isothiazolin-3-one (CMIT)/2-Methyl-4-isothiazolin-3-one (MIT): in vitro absorption of CMIT from an aqueous solution and three formulations through human epidermis, Central Toxicology Laboratory Study N°: JV1870, Rohm and Haas Report N°: 05RC-055, October 20, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2.c/01:	[redacted]	1997	14C-Kathon biocide toxicokinetic study in rats, Rohm and Haas Company, Rohm and Haas Report N° 97R-1058, March 14, 1997, Unpublished.	Y(i)	Rohm and Haas
A6.3.1/01:	[redacted]	1984	Kathon™ 886 MW: one month oral toxicity study in rabbits, Rohm and Haas Company, Rohm and Haas Report N° 84R-095, August 31, 1984, Unpublished.	Y(i)	Rohm and Haas
A6.4.1.a/01:	[redacted]	1982	Kathon™ 886 NAR three month rat drinking water study and one generation reproduction study, Rohm and Haas Company, Rohm and Haas Report N° 81R-162, September 9, 1982, Unpublished.	Y(i)	Rohm and Haas

A6.4.1.a/02:	[redacted]	1975	RH-886T, RH-35,375 and RH-00,345: three month subchronic oral safety evaluation study in rats (metabolite). [redacted] Study N°: 285-010, Rohm and Haas Report N°: 75RC-1001 (February 17, 1975), Unpublished.	Y(ii)	Rohm and Haas
A6.4.1.b/01:	[redacted]	1975	RH-886: Three month subchronic oral safety evaluation study in Beagle dogs, [redacted] Study N° 285-008, Rohm and Haas Report N° 75RC-1002, February 19, 1975, Unpublished.	Y(ii)	Rohm and Haas
A6.4.2/01:	[redacted]	1982	Kathon™ 886 MW: 90-day percutaneous toxicity study in rabbits. Rohm and Haas Company, Rohm and Haas Report N° 80R-119, August 31, 1982, Unpublished.	Y(i)	Rohm and Haas
A6.4.3/01:	[redacted]	1984	Kathon™ 886 MMPA Process: thirteen-week inhalation toxicity study in rats, Rohm and Haas Company, Rohm and Haas Report N° 82R-245, December 10, 1984, Unpublished.	Y(i)	Rohm and Haas
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A6.2-02	[redacted]	2000	(^{14}C)-CIT and (^{14}C)-MIT: Characterisation of metabolites following oral administration to the rat, [redacted] Study No.: 1154/70, 19-12-00 GLP, Unpublished	Yes	Thor GmbH
A6.2-03	[redacted]	1982	^{14}C-kathon 886 disposition after percutaneous application to male rats. Rohm and Haas Company, Report no. 82R-21 (letter of access included) GLP, Unpublished	Yes	Thor GmbH (Rohm and Haas)
A6.2-04	[redacted]	1986	Absorption and disposition of ^{14}C-labelled Kathon® biocide, a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one, following intravenous or dermal administration to male Sprague-Dawley rats. Fd. Chem.Toxic., Vol.24, 1, pp43-49 Published	No	-
A6.2-05 (See A7.1.2-02)	Krzeminski	1975a	Fate of Microbicidal 3-isothiazolone Compounds in the Environment: Products of Degradation. J.Agric. Food Chem.,Vol 3, 6(1975) 1068-1075.	No	na
A6.2-06 (See A7.1.2-03)	Krzeminski	1975b	Fate of Microbicidal 3-isothiazolone Compounds in the Environment: Modes and rates of dissipation J.Agric. Food Chem.,Vol 3, 6(1975) 1060-1068.	No	na
A6.2-07	CIR	1992	Final report on the Safety assessment of Methylisothiazolinone and Methylchloroisothiazolinone. *Journal of the American college of toxicology*, Vol. 11, 1(1992), pp 75-128 Published		
A6.2-08	Jayjock, M.A.	1996	Formulation Effect on the Dermal Bioavailability of Isothiazolone Biocide Fd. Chem. Toxic. Vol 34(3), 1996	No	-
A6.2-09	Søderlund, E.	1992	Kathon. IN: Healt effects of selected chemicals – volume 2.	No	-

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			Nord 1993, 29.		
A6.4.1-01	[redacted]	1982a	Kathon 886 Three month rat drinking water study and one generation reproduction study. Rohm and Haas Company, Study No.: 81P-398 (letter of access included) GLP, Unpublished	Yes	Thor GmbH (Rohm and Haas)
A6.4.1-02	[redacted]	1998a	Acticide 14: 13 Week Oral (Dietary Administration) Toxicity Study in the Dog, [redacted] Study No.: 1154/58, 01-02-98 GLP, Unpublished	Yes	Thor GmbH
A6.4.1-03	[redacted]	1998b	Acticide 14: Pilot (dietary administration) study in the Dog. [redacted] Study No.: 1154/57-1050 GLP, Unpublished	Yes	Thor GmbH
A6.4.1-04	[redacted]	1994	ACTICIDE 14: 14-day oral (gavage) dose range-finding study in the female rat + amendment [redacted], Study No.: 1147-1154-004 GLP, Unpublished	Yes	Thor GmbH
A6.4.2-01	[redacted]	1994	Acticide 14: 90 Day Dermal Subchronic Toxicity Study to the Rat, [redacted] Report no: 1127-1154-002, 13-06-94 GLP, Unpublished	Yes	Thor GmbH
A6.4.2-02	[redacted]	1994a	ACTICIDE 14: 14-day dermal dose range-finding study in the rat + replaced pages [redacted], Study No.: 1127-1154-001 GLP, Unpublished	Yes	Thor GmbH
A6.5-01 (See A6.7-01)	[redacted]	1994b	Kathion Biocide: 24-month drinking water chronic/oncogenic study in rats. Rohm and Haas Company, Study No.: 91R-074 (letter of access included) GLP, Unpublished	Yes	Thor GmbH (Rohm and Haas)
A6.6.1-01	Clare CB	1994	Study to Determine the Ability of Acticide 14 to Induce Mutation in Five Histidine-Requiring Straints of Salmonella Typhimurium, Hazleton Europe Study no: 1154/10R, 29-06-94 GLP, Unpublished	Yes	Thor GmbH
A6.6.1-02	Poth, A.	1992	Salmonella typhimurium: Reverse mutation assay with ACTICIDE 14. CCR Study no: 269201 GLP, Unpublished	Yes	Thor GmbH
A6.6.2-01	Marshall R	1994	Study to Evaluate the Chromosome Damaging Potential of Acticide 14 by	Yes	Thor

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			its Effects on Cultured Human Peripheral Blood Lymphocytes using an in Vitro Cytogenetics Assay, Hazleton Europe Study no: 1154/11, GLP, Unpublished		GmbH
A6.6.3-01	[redacted]	1994	Study to Determine the Ability of Acticide 14 to Induce Mutations at the Thymidine Kinase (tk) Locus in Mouse Lymphoma L5178Y Cells using a Fluctuation Assay, Hazleton Europe Study no: 1154/15, GLP, Unpublished	Yes	Thor GmbH
A6.6.4-01	[redacted]	1997	Acticide 14: Induction of Micronuclei in the Bone Marrow of Treated Mice. [redacted] Study No.: 1154/63, Report No.: 1154/63-1052, 13-03-97 GLP, Unpublished	Yes	Thor GmbH
A6.6.4-02	[redacted]	1994	Study to Evaluate the Potential of ACTICIDE 14 to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice, [redacted] Study no: 1154/23, 29-06-94 GLP, Unpublished	Yes	Thor GmbH
A6.6.5-01	[redacted]	1994	Study to Evaluate the Potential of ACTICIDE 14 to Induce Unscheduled DNA Synthesis in Rat Liver Using an In Vivo/In Vitro Procedure, [redacted] Study no: 1154/, 30-06-94 GLP, Unpublished	Yes	Thor GmbH
A6.7-01	[redacted]	1994	Kathion Biocide: 24-month drinking water chronic/oncogenic study in rats. Rohm and Haas Company, Study No.: 91R-074 (letter of access included) GLP, Unpublished	Yes	Thor GmbH (Rohm and Haas)
A6.8.1-01	[redacted]	1994	ACTICIDE 14 - Oral (Gavage) Teratogenicity Study in the Rat, [redacted] Report no: 1178-1154-003, 26-05-94 GLP, Unpublished	Yes	Thor GmbH
A6.8.1-02	[redacted]	2002	Prenatal Development Toxicity Study of ACTICIDE 14 in Rabbits, [redacted] Study No.: 3494, 15-05-2002 GLP, Unpublished	Yes	Thor GmbH
A6.8.1-03	[redacted]	1992	Kathon Biocide: oral (gavage) developmental toxicity study in rabbits. Rohm and Haas Company, Study No.:	Yes	Thor GmbH (Rohm and

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			91R-074 (letter of access included) GLP, Unpublished		Haas)
A6.8.2-01	[redacted]	1998	Two generation Oral (Gavage) Reproduction Toxicity Study in the Rat (One Litter Per Generation) [redacted] Study No.: 1154-067, Report No: 1413-1154-06, 13-11-98 GLP, Unpublished	Yes	Thor GmbH
A6.8.2-02 See A6.4.1-03	[redacted]	1982	Kathon 886 Three month rat drinking water study and one generation reproduction study. Rohm and Haas Company, Study No.: 81P-398 (letter of access included) GLP, Unpublished	Yes	Thor GmbH (Rohm and Haas)
A6.12-01	Kapahnke, W.	2007	Medical data for CIT/MIT Thor GmbH GLP not applicable, Unpublished	Yes	Thor GmbH
A6.14-01	San RHC, VanDyke MR	2005	n-Methyl Malonamic Acid: Bacterial Reverse Mutation (Ames) Assay, BioReliance AB13CE.503.BTL, (R&H 05RC045), 09.09.2005, GLP/unpublished report	Yes	Thor GmbH (Rohm and Haas)
A6.14-02	Chapdelaine JM	2003	n-Methyl Malonamic Assay: Local Lymph Node Assay, Calvert Laboratories 0787XR07.001(R&H 02RC049), 08.08.2003, GLP/unpublished report	Yes	Thor GmbH (Rohm and Haas)
A7.1.1.1.1-01	Geffke, T	2002a	Acticide 14- Hydrolysis as a function of pH Dr. U.Noack-Laboratorium Report No: CPH80192 GLP, Unpublished	Yes	Thor GmbH
A7.1.1.1.1-02	Lucas, T.	1996a	(14C)-ACTICIDE 14: Hydrolytic stability Corning Hazleton GmbH Report No.: 1225-1154-043. GLP, Unpublished	Yes	Thor GmbH
A7.1.1.1.2-01	Purser, D.	1998	(14C)-Acticide 14: Photodegradation in Sterile, Aqueous Solution Covance, Report no. CHE 1154/60-D2142 GLP/Unpublished report	Yes	Thor GmbH
A7.1.1.1.2-02	Hamwijk, C.	2007a	Structural elucidation of degradation products from the photodegradation of 5-chloro-2-methyl-2H-isothiazol-3-one (CIT, CAS # 26172-55-4) TNO Quality of Life Report no. V6280/02 GLP/Unpublished report	Yes	Thor GmbH

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A7.1.1.1.2-03	Hamwijk, C.	2007b	Structural elucidation of degradation products from the photodegradation of 2-methyl-2H-isothiazol-3-one (MIT, applied as aqueous formulation ACTICIDE® M 20) TNO Quality of Life Report no. V6264/04 GLP/Unpublished report	Yes	Thor GmbH
A7.1.1.1.2-04	Hamwijk, C.	2007c	Structural elucidation of degradation products from the photodegradation of 2-methyl-2H-isothiazol-3-one (MIT, applied as aqueous formulation ACTICIDE® M 20) and 5-chlor-2-methyl-2H-isothiazol-3-one (CIT, CAS# 26172-55-4) TNO Quality of Life Report no. V7137 GLP/Unpublished report	Yes	Thor GmbH
A7.1.1.2.1-01	Noack M.	2002a	Acticide 14: Ready Biodegradability Closed Bottle Test. Dr. U. Noack-Laboratorium, Project No. 001025TS, Study No. AFW80191, 20 January 2002. GLP/ unpublished report	Yes	Thor GmbH
A.7.1.1.2.3-01	Hamwijk,C. and H. Oldersma	2005	Determination of the biodegradability of ACTICIDE® 14 in natural seawater by a Closed Bottle method (OECD Guideline No. 306), TNO Quality of Life, Report V6411/03, 16 November 2005 GLP/ unpublished report	Yes	Thor GmbH
A 7.1.2-01	Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers	2003	Opinion concerning update of Entry no. 39 of Annex VI to Directive 76/768/EEC on cosmetic products: mixture of 5-Chloro-2-methyl-isothiazolin-3(2H)-one and 2 methylisothiazolin-3(2H)-one SSCNFP/0670/03, final COLIPA no. P56, 24-25 June 2003	No	na
A 7.1.2-02	Krzeminski, S.F.	1975a	Fate of Microbicidal 3-isothiazolone Compounds in the Environment: Products of Degradation. J.Agric. Food Chem.,Vol 3, 6(1975) 1068-1075.	No	na
A 7.1.2-03	Krzeminski, S.F.	1975b	Fate of Microbicidal 3-isothiazolone Compounds in the Environment: Modes and rates of dissipation J.Agric. Food Chem.,Vol 3, 6(1975) 1060-1068.	No	na

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A 7.1.2.1.1-01	Fiebig, S.	2002	Acticide 14: Simulation Test- Aerobic Sewage Treatment Dr. U. Noack-Laboratorium, Project No. 001025TS, Study No. ACU80191, 29-01-2002 GLP/ unpublished report	Yes	Thor GmbH
A 7.1.2.1.1-02	Hanstveit, R.	2007a	Activated sludge die away biodegradation test with [14C]-Methyl-2H-isothiazol-3-one (MIT, CAS# 2682-20-4), TNO, V6264/05, draft, 2 February 2007 GLP/ unpublished report	Yes	Thor GmbH
A7.1.2.2.1-01	Hamwijk, C. and R.K.H. Cremers,	2007d	The determination of the degradation of 5-chloro-2-methyl-4-isothiazol-3-one (CIT, CAS # 26172-55-4) in seawater (OECD guideline 309), TNO Quality of Life, report nr. V6280/03, July 2007 GLP/ unpublished report	Yes	Thor GmbH
A 7.1.2.2.1-02	Hamwijk, C. and R.K.H. Cremers	2007	The determination of the degradation of 2- Methyl-2H-isothiazol-3-one (MIT, CAS # 2682-20-4) in seawater (OECD guideline 309), TNO Quality of Life, report nr. V6264/02, 13 March 2007 GLP/ unpublished report	Yes	Thor GmbH
A 7.1.2.2.2-01	Noorloos, B. van	2007a	Aerobic degradation of 14C-CIT (5-chloro-2-methyl-[4,5-14C]-isothiazol-3-one) in two water/sediment systems, NOTOX B.V., Project no. 416508, October 2007 GLP/unpublished report	Yes	Thor GmbH
A7.1.2.2.2-02	Noorloos, B. van	2007b	Aerobic degradation of 14C-MIT (5-chloro-2-methyl-[4,5-14C]-isothiazol-3-one) in two water/sediment systems, NOTOX B.V., Project no. 416497, October GLP/unpublished report	Yes	Thor GmbH
A7.1.2.2.2-03	Lucas, T.	1996b	(14C)-ACTICIDE 14: degradation and retention in one water-sediment system, CORNING Hazleton GmbH, study no. 1154-042. GLP/unpublished report	Yes	Thor GmbH
A7.1.3-01	Geffke, Th	2002b	Acticide 14 – Estimation of the Adsorption Coefficient Koc on Soil and Sewage Sludge using High Performance Liquid Chromatography (HPLC), Dr Noack laboratorium, study no. CAH80192 GLP/ unpublished	Yes	Thor GmbH

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A 7.1.3-02	Hamwijk, C.	2007e	Expert statement: Adsorption of 2-methyl-2H-isothiazol-3-one (MIT) to soil and sediment, TNO Quality of Life, report no. 6264/06, July 2007. Non GLP/ unpublished	Yes	Thor GmbH
A7.2.1-01	Oldersma, H. and F.G.C. Salmon	2007a	Study for the determination of the degradation of 5-chloro-2-methyl-2H-isothiazol-3-one (CIT, CAS# 26172-55-4) in soil (OECD 307), TNO Quality of Life, report nr. V6280/01, July 2007 GLP/unpublished report	Yes	Thor GmbH
A7.2.1-02	Oldersma, H. and F.G.C. Salmon	2007b	Study for the determination of the degradation of 2-Methyl-2H-isothiazol-3-one (MIT, CAS # 2682-20-4) in soil (OECD 307)., TNO Quality of Life, report nr. V6264/03, September 2007 GLP/unpublished report	Yes	Thor GmbH
A7.2.3.1-01	Salmon, F.G.C and Cremers, R.K.H	2007	A study on the adsorption of [14C]-5-chloro-2-methyl-2H-isothiazol-3-one in five soil types and two sediment types (OECD 106) using sterilized soil and sediment., TNO, V6280/04, September 2007 GLP/unpublished report	Yes	Thor GmbH
A7.3.1-01	Hanstveit R.	2006b	Determination of the photolysis in air of 5-chloro-2-methyl-4-isothiazolin-3-one (CIT) and 2-methyl-2H-isothiazol-3-one (MIT) by Atkinson calculation (SETAC Europe (1995) Guideline). TNO Quality of Life, Report no. V6411/01, September 2006 GLP/ unpublished report	Yes	Thor GmbH
A7.4.1.1-01	Wyness, L.E.	1994a	Acticide 14: Acute toxicity to Oncorhynchus mykiss. Hazleton Europe; Report no. 1154/8R-1018 GLP/ unpublished report	Yes	Thor GmbH
A7.4.1.1-02	Wyness, L.E.	1994b	Acticide 14: Acute toxicity to Lepomis macrochirus. Hazleton Europe; Report no. 1154/14R-1018 GLP/ unpublished report	Yes	Thor GmbH

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A7.4.1.1-03	[redacted]	1998	Flow-through acute toxicity of Acticide 14 to the Sheepshead minnow Cyprinodon variegatus [redacted] Inc. Study no. 1405-TO. GLP/ unpublished report	Yes	Thor
A7.4.1.2-01	Mattock, S.D.	1996	Acticide PT: Acute immobilisation and reproduction test with Daphnia magna CORNING Hazleton (Europe); Report no. 1154/56 GLP/ Unpublished report	Yes	Thor
A7.4.1.2-02	Boeri, R.L. Magazu, J.P. and Ward, T.J	1998b	Flow-through acute toxicity of Acticide 14 to the Mysid, Mysidopsis bahia. T.R. wilbury Laboratories, Inc. study no. 1406-TO. GLP/ Unpublished report	Yes	Thor GmbH
A7.4.1.2-03	Boeri, L.B., Magazu, J.P. and Ward, T.J.;	1998c	Flow-through mollusc shell deposition test with Acticide 14 T.R. Wilbury Laboratories, Inc.; Study no. 1407-TO; April 13, 1998 GLP/unpublished	Yes	Thor GmbH
A7.4.1.3-01	Wyness, L.E.	1994e	Acticide 14: Effect on the growth and reproduction of non-target aquatic plants. Hazleton Europe, report no. 1154/6-1018 GLP/ unpublished report	Yes	Thor
A7.4.1.3-02 (see A7.4.13-01)	Wyness, L.E.	1994c	Acticide 14: Effect on the growth and reproduction of non-target aquatic plants. Hazleton Europe, report no. 1154/6-1018 GLP/ unpublished report	Yes	Thor GmbH
A7.4.1.3-05	Scheerbaum, D.	2008	ACTICIDE® 14: Alga, Growth Inhibition Test with Pseudokirchneriella subcapitata, 96 h, Dr.U.Noack-Laboratorien; Report no. SPO120891; 08.08.2008, GLP, unpublished	Yes	Thor GmbH
A7.4.1.4-01	Noack, M.	2002c	ACTICIDE ® 14. Respiration test with activated sludge. Dr. U.Noack-Laboratorium Report No: BBR86592 GLP, Unpublished report	Yes	Thor GmbH

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A7.4.2	Verhaar, H.J.M.	2007b	Bioconcentration behaviour of ACTICIDE® 14 (CIT/MIT 3:1), statement. ENVIRON Netherlands, report no. 77T-BPD2007105, July 2007 Expert statement, non GLP, unpublished	Yes	Thor GmbH
A7.4.3.2-01	[redacted]	1999b	Acticide 14: Fish (Rainbow trout), juvenile growth test, 28 d (semi-static). [redacted], Study no. FWR61772; GLP/ unpublished report	Yes	Thor GmbH
A7.4.3.4-01 (see A7.4.1.2-01)	Mattock, S.D.	1996	Acticide PT: Acute immobilisation and reproduction test with Daphnia magna. CORNING Hazleton (Europe) ; report no. 1154/56 GLP/ Unpublished report	Yes	Thor GmbH
A7.4.3.5.1-01	Scheerbaum, M.	1999	ACTICIDE 14: Effects on the development of Chironomus riparius in a water-sediment system. Dr. U. Noack-Laboratorium, Study no. IZS61773, 08-07-1999 GLP/unpublished	Yes	Thor GmbH
A 7.4.3.5.2-01 = A 7.4.1.3-02					
A7.5.1.1-01	Hamwijk, C. and H. Oldersma	2006b	An assessment of the effects of ACTICIDE® 14 (an aqueous 14% formulation of CIT/MIT 3:1) on the nitrogen transformation and carbon mineralization activity of soil micro-organisms. (OECD 216 and 217 Guidelines), TNO Quality of Life, report nr. V6411/02, 27 February, 2006 GLP/unpublished	Yes	Thor GmbH
A7.5.1.2-01	Noack, M.	2001	Acticide 14: Earthworm (Eisenia fetida), Acute toxicity test in artificial soil, Dr. U. Noack-Laboratorium, Study no. RRA80191. GLP/ unpublished report	Yes	Thor GmbH
A 7.5.1.3-01	Wyness, L.E.	1994f	Acticide 14: Terrestrial Plants, Growth Test Hazleton Europe, report no. 1154/22-1018, 01-09-1994 GLP/ unpublished report	Yes	Thor GmbH

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B 2.2-01 (confidential)	Anonymous	2007	Sales specification ACTICIDE 14	Yes	Thor GmbH
B3.7-01	Rüb, B.	1993	Determination of stability of Acticide 14 Thor Chemie GmBH, Germany. Report no. 9301-BR-4 Not GLP, Unpublished	Yes	Thor GmbH
B5.10-1	Gillatt J	2007	ACTICIDE®14: Evaluation of Microbiological Efficacy for Product Type 13, Thor technical service report no. 23163, 05-06-2007, Non-GLP/unpublished	Yes	Thor GmbH
B5.10-2	Grabbe R	2008h	ACTICIDE®14: Examination of microbiological efficacy for Product Type 13, Thor Technical Service Report No. 27934, 08-12-2008. Non-GLP/unpublished	Yes	Thor GmbH
B5.10-3	Grabbe R	2008i	ACTICIDE®14: Examination of microbiological efficacy for Product Type 13, Thor Technical Service Report No. 20608/24487, 27-11-2008. Non-GLP/unpublished and company confidential	Yes	Thor GmbH
B6.6-01 (confidential)	Hemmerling H	2007	Measurement of the concentration of airpollutants in the workplace within the framework of prevention based on SGB VII (German Social Security Code), BG Chemie 1140010072204, non-GLP, unpublished	Yes	Thor GmbH
B6.6-02 (confidential)	Hemmerling H	2007	Measurement of the concentration of airpollutants in the workplace within the framework of prevention based on SGB VII (German Social Security Code), BG Chemie 1140127062204, non-GLP, unpublished	Yes	Thor GmbH
B6.6-03 (confidential)	Hemmerling H	2007	Measurement of the concentration of airpollutants in the workplace within the framework of prevention based on SGB VII (German Social Security Code), BG Chemie 1140118072204, non-GLP, unpublished	Yes	Thor GmbH
B6.7-01 II-B	Rueb B	2001	Monitoring Study in a Paper Factory. Thor GmbH, Report no. 0013-BR-S, 09-03-2001 GLP not applicable / unpublished	Yes	Thor GmbH

B8-01	Anonymous	2005	MSDS ACTICIDE SPX Thor GmbH GLP not applicable, Unpublished	No	Thor GmbH
B8-02	Anonymous	2005	PDS ACTICIDE SPX Thor GmbH GLP not applicable, Unpublished	No	Thor GmbH