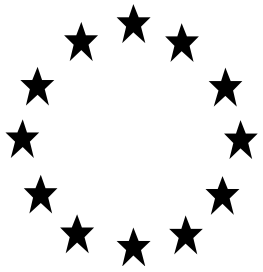
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



2-Methyl-2H-isothiazol-3-one

Product type 12
(Slimicides)

April 2017
Slovenia

Contents

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. PROCEDURE FOLLOWED

This assessment report has been established as a result of the evaluation of the active substance 2-methylisothiazol-3(2*H*)-one in product-type 12 (Slimicides), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

2-Methylisothiazol-3(2H)-one (CAS no. 2682-20-4) was notified as an existing active substance, by Thor GmbH, hereafter referred to as the applicant, in product-type 12.

Commission Regulation (EC) No 1062/2014 of 4 August 2014 lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

On 5 November 2008 the Slovenian competent authority received a dossier from Thor GmbH. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 18 May 2009.

On 7 April 2016, the Rapporteur Member State submitted to the Agency (ECHA) and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

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 REPORT

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of 2-methylisothiazol-3(2*H*)-one for product-type 12 and, should it be approved, to facilitate the authorisation of individual biocidal products. 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.

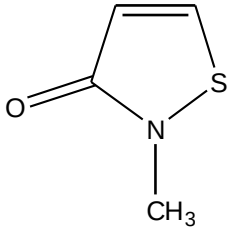
For the implementation of the common principles of Annex VI, the content and conclusions of the assessment report, which is available from the website of ECHA shall be taken into account.

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 for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. PRESENTATION OF THE ACTIVE SUBSTANCE

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

Main constituent	
IUPAC or EC name	2-methylisothiazol-3(2*H*)-one
Common name, synonyms	MIT, MI, methylisothiazolinone, 2-methyl-4-isothiazoline-3-one, 2-methyl-2H-isothiazol-3-one
EC number	220-239-6
CAS number	2682-20-4
Index number in Annex VI of CLP	-
Minimum purity / content	950 g/kg
Structural formula	

Relevant impurities and additives		
IUPAC name or chemical name or EC name	**Maximum concentration in g/kg**	**Index number in Annex VI of CLP**
5-chloro-2methyl-2*H*-isothiazol-3-one (C(M)IT)	1 g/kg (dry weight)	613-167-00-5

The main identification characteristics and the physico-chemical properties of MIT are given in Appendix I to this document.

The methods of analysis for the active substance as manufactured and for the determination of impurities and additives have been validated. Applicant has acceptably validated methods for the analysis of MIT in surface water, air and simulated food (acetic acid, ethanol, olive oil). The limits of quantification were 0.1 µg/l in water, 0,26 µg/m3 in air and 0.025 µg/ml in simulated foods. The waiving of other analytical methods to determine MIT in soil and sediment by the applicant was accepted based on the properties and behaviour of the substance (DT50 < 3 days, DT_{90} was not calculated due to the rapid degradation).

2.1.2. Intended Uses and Efficacy

The assessment of the biocidal activity of the active substance demonstrates that MIT has a sufficient level of efficacy against the target microorganisms (bacteria and fungi) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

MIT is intended to be used by industrial and professional users as a slimicide for preservation of aqueous products in paper mills against harmful microorganisms in end concentration of 15 mg a.s./l applied by shock or continuous dosing. In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.3. Classification and Labelling

The opinion proposing harmonised classification and labelling (CLH) of MIT was adopted by the Committee for Risk Assessment (RAC) on 10 March 2016, but the harmonized classification and labelling in Annex VI of the Regulation (EC) No 1272/2008 (CLP Regulation) has not been amended yet.

The proposed classification and labelling for MIT according to CLP Regulation is:

Classification and labelling in accordance to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox. 2/H330 Acute Tox. 3/H311 Acute Tox. 3/H301 Skin Corr. 1B/H314 Skin Sens. 1A/H317 Aquatic Acute 1/H400 Aquatic Chronic 1/H410
Labelling	
Pictogram codes	GHS06 GHS05 GHS09
Signal Word	Danger
Hazard Statement Codes	H330: Fatal if inhaled H311: Toxic in contact with skin H301: Toxic if swallowed H314: Cause severe skin burns and eye damage H317: May cause an allergic skin reaction H410: Very toxic to aquatic life with long lasting effects
Supplementary hazard statement	EUH071
Specific Concentration limits, M-factors	Skin. Sens. 1A; H317: SCL ≥ 0.0015 % Aquatic acute M-factor: 10 Aquatic chronic M-factor: 1

2.2. SUMMARY OF THE RISK ASSESSMENT

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification and effects assessment

Endpoint	Brief description
Toxicokinetics	A first toxicokinetic study in rats, gavaged with 5 and 50 mg/kg bw ^{14}C-labelled MIT, indicated that 67-73 % of the low dose and 55-58 % of the high dose were absorbed in males and females, respectively, based on the radioactivity detected in urine, cage wash and tissues. In a second toxicokinetic study on bile-cannulated female rats that were administered 50 mg/kg bw ^{14}C-labelled MIT and 53 % was absorbed, when considering the radioactivity recovered in the urine and cage wash. In a third study rats received 50 mg/kg bw ^{14}C-labelled MIT and 67-69 % were absorbed in males and females as indicated by the radioactivity recovered from the urine, cage wash, cage debris and tissues. The lower absorption value 53 %, as determined in the bile cannulated rats and confirmed in another toxicokinetic study, will be used for MIT. MIT is widely distributed in the tissues with higher values detected in the blood and that might account for high levels in the highly vascularized tissues. There is no evidence that MIT would accumulate in the body. Metabolism of MIT in rats is extensive; 23 and 12 metabolites (detected in different dossiers) were observed in the urine and feces of exposed animals. Parent compound was not detected in the urine, bile or feces of treated rats. As shown in two studies major urine metabolite is N- methyl malonamic acid (NMMA) (21-23 % of the dose) and 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl propionamide (10-23 % of the dose) (range from different dossiers). Twenty radioactive components were observed in the bile in low amounts, each accounting for less than 5 % of the dose, with glutathion conjugate of 3-thiomethyl-N-methyl-propionamide accounting for 4.9 % of the dose. The proposed main metabolic pathway of MIT consists of oxidative and reductive cleavage in Phase I, followed by conjugation with mercapturic acid in Phase II. MIT is rapidly excreted from the rat. The main elimination route from the body is urine (53-70 % in 24 hours were observed in different dossiers), while feces (21-37 %) and bile (29 %) excretion are also important for elimination of MIT. The elimination half-life of ^{14}C-labelled MIT form plasma is 3.2-3.9 h at 5 mg/kg bw and 5.1-6.2 h at 50 mg/kg bw. Based on *in vitro* dermal absorption study with various concentrations of MIT in water on human epidermis, dermal absorption value of 67 % was determined for an aqueous solution of MIT.. In the risk assessment of biocidal products (containing 20 and 50 % MIT) 100 % dermal absorption will be used due to corrosive and irritant properties of MIT that may damage skin and alter its penetration. According to the EFSA guidance on dermal absorption (2012) 75 % will be

	used as a dermal penetration value in the risk assessment for MIT preserved cooling and processing liquids.
Acute toxicity	MIT is acutely toxic to rats and mice by the oral route. MIT was acutely toxic after dermal exposure and of low toxicity with no classification required in another study. Since both studies were performed according to the guideline and GLP the more conservative was chosen for the proposed classification regarding toxicity of MIT by dermal route. MIT is acutely very toxic by inhalation.
Corrosion and irritation	MIT is considered to be corrosive to skin and eyes. It is irritant to respiratory tract.
Sensitisation	MIT is a skin sensitizer. Regarding sensitizing potential of MIT specific concentration limit ≥ 0.0015 % for classification H317 (May cause an allergic skin reaction) is proposed.
Repeated dose toxicity	MIT was administered to rats by gavage for 28 and 90 days and via drinking water for 90 days. Dogs were also exposed to MIT through daily diet for 90 days. In rat and dog studies reduced food or/and water consumption were observed, presumably due to palatability problems, and consequently reduced body weight gain. In 90 days rat gavage study increased spleen weight was observed in males in the absence of histopathological findings. The lowest NOAEL derived in the repeated dose studies is 10 mg/kg bw/day in dietary exposed dogs (90 days study). Decreased food consumption and body weight gain was observed at LOAEL, 41 mg/kg bw/day. The 90 days dietary dog study was selected for the risk assessment of systemic effects. Dermal and inhalation repeated dose studies were not performed with MIT. However, the Applicant has submitted studies with the mixture of 5-chloro-2-methyl-2*H*-isothiazolin-3-one with MIT, CMIT:MIT (3:1), that is considered to be more toxic compared to MIT alone. These studies were submitted to demonstrate that systemic effects would be observed at levels exceeding doses that induce local effects at site of first contact. Three months inhalation toxicity study in rats was performed with CMIT/MIT (3:1). NOAEC 0.34 mg/m^3 was derived based on slight rhinitis observed at LOAEC 1.15 mg/m^3. NOAEC for CMIT/MIT (3:1) was used in the risk assessment of local inhalation effects only to demonstrate that inhalation exposure to MIT will not induce adverse effects after repeated inhalation exposure. The use of NOAEC represents the worst case reference value for MIT since CMIT/MIT is considered to be more toxic than MIT alone.
Genotoxicity	MIT produced no evidence of genotoxicity when tested in the battery of *in vitro* and *in vivo* tests.
Carcinogenicity	MIT produced no evidence of genotoxicity when tested in the battery of *in vitro* and *in vivo* tests.
Reproductive toxicity	Teratogenicity of MIT was evaluated in two species. The lowest maternal NOAEL value 10 mg/kg bw/day was derived in rabbits based on dark red areas in the stomach, body weight loss, reduced food consumption and reduced defecation at LOAEL, 30 mg/kg bw/day. Observed effects probably result from the irritation of stomach, which is the site of the first contact after gavage and

	therefore these effects are not used for the systemic risk assessment. Reduced food intake and reduced body weight gain were also observed in both rat studies, while in one red areas of glandular portion of stomach were observed additionally. The lowest foetal NOAEL, 30 mg/kg bw/day, was derived in the rabbit teratogenicity study. This was the highest dose tested. MIT is not teratogenic in rats and rabbits; MIT did not affect intrauterine growth and survival of foetuses, number of resorptions, fetal body weight, sex ratio, and it did not induce increase of skeletal or soft-tissue variations and malformations. However, in one rat study increased incidence of dilated cerebral ventricles, unossified metatarsals and cervical vertebral bodies were observed at maternally toxic doses. In a two generation reproduction study in the rat it was demonstrated that MIT is not toxic for reproduction. Parental, F1 and F2 generation NOAEL was 15 mg/kg bw/day in males and 22 mg/kg bw/day in females. At LOAEL, 69 and 93 mg/kg bw/day for males and females, respectively, decreased body weight gain was observed on weeks 1-5 of each generation, during middle/late phase of gestation and lactation or throughout the generation, decreased food consumption throughout the pre-breeding period, middle-to-late gestation and middle-to-late lactation in all generations, and decreased mean offspring body weights on PND 7-21 (F1) and PND 14-21 (F2).
Neurotoxicity	No signs of neurotoxic activity were observed in any Study performed with MIT. Additionally, MIT does not belong to the group of chemicals that act as neurotoxicants.
Immunotoxicity	No immunotoxicity study was performed with MIT.
Disruption of the endocrine system	MIT did not induce any effect that would be correlated to the endocrine disruption mechanism in any of performed studies. It did not affect reproduction or development of treated animals.
Other effects	Several human skin sensitization studies and one cumulative irritation study were conducted with MIT. 100- 600 ppm MIT was used in the clinical trials. At 400 and 500 ppm 1/116 and 1/210 volunteers, respectively, showed signs of skin sensitization. However, at 600 ppm no skin reactions were observed in 214 exposed volunteers. In cumulative skin irritation study volunteers were exposed to 50, 100, 250, 500 and 1000 ppm MIT for 21 days. Below and including 500 ppm no signs of irritation were observed. At 1000 ppm slight signs of skin irritation were observed after 17 applications. Skin sensitization was observed in 2 individuals induced with 1000 ppm MIT. Based on the results of submitted studies the NOAEC 600 ppm or 0.06 % for skin sensitization was originally proposed as a specific concentration limit for classification. MIT was introduced as an individual preservative for industry products in year 2000 and for cosmetic products in 2005. First cases of skin sensitising reactions following occupational exposure emerged in 2004. In 2010 the skin contact allergy was reported from the cosmetic use. Several reports on the increasing

	sensitization towards MIT in contact dermatitis patients followed. The potential sources of MIT exposure are occupational exposure, cosmetic products and household products. MIT alone has been tested in several patch tests in patients with contact dermatitis. The ratio of patients with contact dermatitis that positively responded to patch test with MIT is increasing over the last years in several European countries and also in the USA. The levels eliciting sensitizing skin reactions to MIT in dermatitis patients in patch tests ranged from 200 to 2000 ppm. Currently the use of 100 ppm as a maximum concentration in cosmetic products is allowed. Due to reports on increasing sensitization towards MIT the Scientific Committee on Consumer Safety has released the Revision of the opinion on methylisothialzolinone (P94) (SCCS/1521/13) in 2013. The SCCS is of the opinion that the rise of MIT contact allergy is primarily caused by increasing consumer exposure to MIT from cosmetic products. After reviewing all the available data, it was agreed that the maximum concentration of 100 ppm in cosmetic products is not safe for the consumer. For leave-one products no safe concentrations of MIT for induction of contact allergy or elicitation have been adequately demonstrated. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015 %) MIT is considered safe for the consumer from the view of induction of contact allergy. However no information is available on elicitation. Based on the available information on skin sensitising potential from submitted animal studies and case reports in humans, taking into account the CMIT/MIT SCL the SCL for MIT is 15 ppm.

Critical endpoints

Systemic effects

Duration	Study	Route	Relevant effects	NOAEL/ LOAEL	References to DOC III
Acute	Acute oral toxicity in rats	Oral	Clinical signs (passiveness, ataxia, lethargy, diarrhea or soft feces, scant or no feces, lacrimation, piloerection and ptosis)	LD_{50} = 120 – 328 mg/kg bw	A6.1.1/01, A6.1.1/02, A6.1.1/03, A6.1.1-1
	Acute dermal toxicity in rats	Dermal	Clinical signs (scant or no feces, passiveness and ataxia), decreased body weight	LD_{50} = 242 mg/kg bw	A6.1.2/01
	Acute inhalation toxicity in rats	Inhalation	Clinical signs (tremor, dyspnoea, activity decrease, squatting position, piloerection,	LC_{50} = 0.11-0.19 mg/l	A6.1.3a/01, A6.1.3a/02, A6.1.3-1

			increased respiration rate) laboured breathing		
Medium-term	90-days dietary rat study, rabbit developmental study	Oral	Reduced body weight, reduced food and water consumption	NOAEL 10 mg/kg bw/day	A6.4.1b/01, A6.8.1b/01
Long-term	None	n.a.	n.a.	n.a.	n.a.

Local effects

Route	**Effect**	**Study**	**Classification**	**Hazard category[1]**
Dermal	Corrosion	2 skin corrosion studies in NZ Rabbits, Epiderm (EPI-2) human epidermal construct study	H314	Skin Corrosive 1C
	Skin sensitisation	Guinea pig test Buehler method, 2 Magnusson-Klingmann studies, 1 LLNA assay in mice	H317	Skin Sens. 1A
Respiratory	Respiratory irritation	2 acute inhalation toxicity studies in rats, 1 upper airway irritation test	/ Supplementary hazard statement: EUH071	/

Absorption

Route	Study	Test substance	Concentration of test substance	Applicability (concentration ranges)	Value
Oral	Yes	MIT (aq. dilution)	5 and 50 mg/kg bw	Acceptable	53 %
Dermal	Yes	MIT (aq. dilution)	52.2, 104 and 313 µg/l	Lower concentration of MIT was tested compared to the proposed use, but due to different composition of slimicides the default values should be used (EFSA guidance, 2012)	100 % for the concentrate 75 % default value, based on EFSA guidance on dermal absorption (2012) for ≤ 5 % a.s.
Inhalation	No	n.a.	n.a.	n.a.	100 %

Reference values

	Study	NOAEL/ LOAEL	Overall assessment factor	Value
$AEL_{short-term}$	Rabbit developmental study, 90-days dog study	10 mg/kg bw/day	100, 0.53 correction factor for oral abs.	0.053 mg/kg bw/day
$AEL_{medium-term}$	Rabbit developmental study, 90-days dog study	10 mg/kg bw/day	100, 0.53 correction factor for oral abs.	0.053 mg/kg bw/day
$AEL_{long-term}$	Rabbit developmental study, 90-days dog study	10 mg/kg bw/day	200, 0.53 correction factor for oral abs.	0.027 mg/kg bw/day
ARfD	Rabbit developmental study	10 mg/kg bw/day	100	0.10 mg/kg bw/day
ADI	90-days oral dog study	10 mg/kg bw/day	200	0.05 mg/kg bw/day

Short-term AEC_{inh} *	90-days rat study	0.34 mg/m^3	8	0.043 mg/m^3
Short-term AEC_{inh} *	90-days rat study	0.34 mg/m^3	8	0.043 mg/m^3
Short-term AEC_{inh} *	90-days rat study	0.34 mg/m^3	16	0.021 mg/m^3

*- AEC_{inh} is proposed based on the NOAEC from the repeated dose inhalation study with CMIT/MIT (3/1).

2.2.1.1. Exposure assessment and risk characterisation

Scenario description

Summary table: scenarios			
Scenario number	**Scenario**	**Primary or secondary exposure Brief description of scenario**	**Exposed group**
1.	Automated loading into the sump	Primary exposure The biocidal product is supplied in plastic cans, PVC drums and IBCs container. The TNsG (TNsG, part 2, 2002, type 12 Slimicides, pages 98 - 100) indicates that biocidal product is added to these systems by dosimeter (automated system) from drums, IBC's or on-site bulk storage tanks. Some facilities may add biocidal product manually as a measured dose (e.g., bucket). It is stated by the applicant in the dossier that the biocidal products is applied to the recycled paper process water via automated dosage therefore only this kind of loading will be addressed in the exposure assessment and application will be limited only to an automated dosing. The drum containing the biocidal product has to be connected to an automated dosing system weekly to monthly and this takes approximately 5 minutes as it is stated by the applicant based on outcome of the questionnaire on MIT usage pattern sent to representative end-users. Also the TNsG (2002) suggests frequency for changing the reservoir of once per week with task duration of 5 minutes for systems with automatic dosimeters. The exposure during automated transfer is expected to be very low and exceptionally can occur through disconnecting an empty drum and reconnecting a full drum of MIT 20%. These operations may be conducted by water treatment service companies. Since the exposure during the connection process is expected to be very low, the professionals wil not be considered separately.	Professionals

2.	Application - process operation	Primary exposure No human exposure is foreseen, since the only application is during loading phase of the product (see Scenario 1). The biocidal product is applied automatically via a dosing system (automated pump and timer) under natural room ventilation as shock treatment with an initial ACTICIDE® M 20 S concentration of 15 ppm MIT. Dosing duration is 20 - 30 min applied 4 times per day. In this process step no worker is involved. Therefore, the loading and the application would be considered as one task.	Professionals
3.	Post application - sampling process liquid (dip slide)	Primary exposure Routine testing of the process water is conducted to monitor for microbial contamination. The TNsG (2002) for PT 12.01 (Slimicides for paper pulp) describes that sampling for microbial counting and examination involves transient hand contact with process water. It is stated by the applicant that professionals take samples from process water daily, but there is no indication provided for the duration and/or frequency of these task in the dossier nor in the TNsG. Applicant provided data for another similar scenario where specially trained operators take water samples for routine analysis of water parameter (chemical/microbiological) for PT11.02 (Preservatives used in recirculating cooling systems). Sample drawing may take 10 minutes what is also in line with description in the TNsG for this product type.	Professionals
4.	Post application – cleaning dispensing pumps and empty conitainers	Primary exposure During certain maintenance operations, professionals can be potentially exposed to process water that has dried on equipment and the concentration of the biocidal product in the dried residues may be above the estimated circulating level (15 pm a.i.). For equipment maintenance tasks, professionals use gloves, waterproof work clothing, eye protection and respiratory equipment if necessary (TNsG, 2002). Duration and frequency are not indicated in the TNsG for equipment maintenance, however it is anticipated that this task could occur 4 hours per day on a daily basis as a worst case assumption.	Professionals

5.	Post application – process equipment maintenance	Primary exposure Maintenance and repair of dosing pumps require the cleaning of these items before dismantling (TNsG, 2002). Drums may be returned or recycled and IBC's are returned to supply company. There is no indication of the frequency and the duration of these tasks in the TNsG nor in the dossier therefore expert judgement has been made considering similar scenario under PT 11.	Professionals
6.	Inhalation of humidified air containing biocidal product	Primary exposure Exposure to humidified air containing residual biocidal product represents a potential secondary inhalation exposure for professionals. Regarding the high solubility of MIT, the vapour pressure and the concentration in water (15 ppm), the quantity of the active substance that can transfer from water to air is extremely low. The Henry's law can be used to estimate approximately the partition of the active substance between the atmosphere and the aqueous phase in equilibrium (worst case): C_{air}/C_{water} = kH/RT. There is no model for assessing exposure to the aerosol part of the paper mill system. As a worst case approach, the exposure to the aerosol of such system is supported to be lower than the application liquid spraying. The worst case value of the different spraying model of the TNsG 2002 has been chosen for the tier 1 assessment. The worst case value 405 mg product/m^3 is from the spraying model 1 page 145 of the TNsG 2002 considering spraying with a compression sprayer at 1 to 3 bars.	Professionals

7.	Dermal exposure from contact with paper	Primary exposure It is stated in the dossier by the applicant that professionals can be exposed to the residues of ACTICIDE® M 20 S bounded to paper since the pulp contains water treated with this biocidal product. A study on determination of the specific migration of MIT into ethanol and heptane from paper manufactured with the biocidal product containing MIT was submitted by the applicant. The study indicates that a maximum total of 0.63 ppm (0.0063 µg/cm^2 paper) MIT is found as residue in paper. However, the study can't be used for assessment of dermal exposure resulting from contact with paper since there is no data on MIT concentration in paper pulps. However, it is likely that due to its high water solubility, MIT is not bound to paper but remains in the water phase and any trace residues present in wet paper will quickly degrade or evaporate during the drying process. Because it is very difficult to assess this exposure eCA chose a reverse scenario approach in order to avoid unrealistic assumptions and get an estimation of magnitude of an exposure through contact with paper.	Professionals/ General public

Exposure calculations

Summary table: systemic exposure from industrial/professional uses				
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake [mg/ kg bw /day]**	**Estimated dermal uptake [mg/ kg bw /day]**	**Estimated total uptake [mg/ kg bw /day]**
Scenario 1 **-** Automated loading into the sump	Tier 1/ no PPE	-	$1.53 \cdot 10^{-2}$	$1.53 \cdot 10^{-2}$
	Tier 2/ PPE	-	$1.53 \cdot 10^{-3}$	$1.53 \cdot 10^{-3}$
Scenario 3- Sampling process liquid (dip slide)	Tier 1/ no PPE	$1.72 \cdot 10^{-8}$	$1.03 \cdot 10^{-4}$	$1.03 \cdot 10^{-4}$
Scenario 4 **-** Process equipment maintenance	Tier 1/ no PPE	$4.12 \cdot 10^{-7}$	$2.48\ 10^{-3}$	$2.48 \cdot 10^{-3}$
Scenario 5 **–** Cleaning dispensing pumps and empty drums	Tier 1/ no PPE	$4.58 \cdot 10^{-6}$	$3.67 \cdot 10^{-2}$	$3.67 \cdot 10^{-2}$
	Tier 2/ PPE	$4.58 \cdot 10^{-6}$	$3.03 \cdot 10^{-3}$	$3.03 \cdot 10^{-3}$

Scenario 6 – Inhalation of humidified air containing biocidal product	Tier 1/ no PPE	$1.06 \cdot 10^{-3}$	-	$1.06 \cdot 10^{-3}$

Conclusion of risk characterisation for industrial/professional user

Scenario, Tier, PPE	**Relevant reference value**	**Estimated uptake** mg/kg bw/d	**Estimated uptake/reference value** (%)	**Acceptable** (yes/no)
Automated loading into the sump, Tier 1, no PPE	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$1.53 \cdot 10^{-2}$	56	Yes
Automated loading into the sump, Tier 2, PPE*	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$1.53 \cdot 10^{-3}$	5.6	Yes
Sampling process liquid (dip slide)	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$1.03 \cdot 10^{-4}$	0.4	Yes
Post application – process equipment maintenance	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$2.48 \cdot 10^{-3}$	9.2	Yes
Cleaning dispensing pumps and empty drums, Tier 1, no PPE	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$3.67 \cdot 10^{-2}$	135.9	No
Cleaning dispensing pumps and empty drums, Tier 2, PPE*	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$3.03 \cdot 10^{-3}$	11.2	Yes
Inhalation of spray from preserved cooling water	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$1.06 \cdot 10^{-3}$	3.9	Yes
Dermal exposure from contact with paper, Tie 1, no PPE	Currently no exposure model is proposed to allow the realistic quantitative estimation of professional exposure during this task. A reverse exposure scenario was used to estimate if the exposure to MIT through contact with paper would result in exceedance of the chronic AEL taking into account combined exposure during other tasks. It was concluded that the exposure to MIT through contact with paper is acceptable.			
Scenarios 1+3+4+5+6: Automated loading (Tier 2) + sampling process liquid (Tier 1) + process equipment maintenance (Tier 1) + cleaning dispensing pump and empty drums (Tier 2) + inhalation of humidified air containing biocidal product (Tier 1)	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$8.20 \cdot 10^{-3}$	30.4	Yes

Scenario, Tier, RPE	Relevant reference value	External inhalation exposure mg /m³ (8 hrs-TWA)	Estimated exposure/ long-term AEC_{inh} (%)	Acceptable (yes/no)
Automated loading into the sump, Tier 1,2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/m³	-	n/a	Yes
Sampling process liquid (dip slide), Tier 1,2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/ m³	$1.03 \cdot 10^{-7}$	4.90×10^{-4}	Yes
Cleaning dispensing pumps and empty drums, Tier 1,2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/ m³	$2.48 \cdot 10^{-6}$	1.18×10^{-2}	Yes
Process equipment maintenance, Tier 1,2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/ m³	$2.75 \cdot 10^{-5}$	1.3×10^{-1}	Yes
Inhalation of spray from preserved paper pulp, Tier 1, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/ m³	$6.35 \cdot 10^{-3}$	30.2	Yes

Scenario, Tier	SCL for dermal effects	Deposit on hands	Acceptable (yes/no)
Automated loading into the sump, Tier 1, no PPE	0.0015 %	20 %	No
Automated loading into the sump, Tier 2, PPE*	0.0015 %	20 %	Yes
Sampling process liquid (dip slide), Tier 1, no PPE	0.0015 %	0.0015 %	No
Sampling process liquid (dip slide), Tier 2, PPE*	0.0015%	0.0015 %	Yes
Process equipment maintenance, Tier 1, no PPE	0.0015 %	0.0015 %	No
Process equipment maintenance, Tier 2, PPE*	0.0015 %	0.0015 %	Yes
Cleaning dispensing pumps and empty drums, Tier 1, no PPE	0.0015 %	20%, 0.2 %	No
Cleaning dispensing pumps and empty drums, Tier 2, PPE*	0.0015 %	20%, 0.2 %	Yes
Dermal exposure from contact with paper, Tier 1, no PPE	0.0015 %	MIT residues in paper	Yes

*- appropriate protective gloves and impermeable coverall

The estimated systemic exposure of professional to MIT is below the reference value during automated loading of ACTICIDE® M 20 S into the sump when RMM for high hazard class chemicals are implemented and professional is wearing protective gloves, impermeable coverall and face mask in order to prevent any contact with MIT. The risk of local dermal and respiratory effects during automated loading into the sump is also considered to be acceptable.

When sampling processing liquids by dip sliding and during process equipment maintenance the professional's exposure is estimated to be below the $AEL_{long\text{-}term}$ and therefore acceptable. The concentration of MIT in processing liquid is at the specific concentration limit for skin sensitisation and thereafter appropriate gloves and impermeable coverall must be used by professionals in order to avoid the risk of local dermal effects.

During cleaning of dispensing pumps and empty drums, sampling process liquids and maintenance of processing equipment professionals must wear appropriate personal protective equipment (gloves, impermeable coverall, face mask) to avoid any contact with residues of ACTICIDE® M 20 S. The systemic exposure of professionals to MIT during these tasks is considered to be acceptable.

Professionals working in the vicinity of processing liquids and paper pulp might be exposed to MIT residues by inhalation of contaminated air in the mill. However, their exposure to MIT is calculated to be below the reference value for systemic and local respiratory effects.

Since realistic quantitative estimation of professional exposure during contact with paper is not possible a reverse scenario was used to estimate if the exposure to MIT during this task would result in exceedance of the chronic AEL taking into account combined exposure during other tasks. It was concluded that the exposure to MIT through contact with paper is acceptable. Professional was not assumed to wear any PPE. In addition, contact with paper does not pose a risk for dermal local effects.

Assuming one person performing different scenarios on the same day, the combined exposure was estimated assuming a person automatically loading ACTICIDE® M 20 S into the sump, monitoring the liquid by slide dipping, maintaining process equipment, cleaning dispensing pumps and empty drums and inhaling MIT residues in air during that day. The combined exposure for systemic effects is considered to be acceptable when ACTICIDE® M 20 S will be used for preservation of processing liquids for production of paper according to the instructions for use.

Conclusion of risk characterisation for non-professional user

The biocidal product ACTICIDE® M 20 S is intended under PT 12 only for professional use.

Conclusion of risk characterisation for secondary (indirect) exposure

Secondary exposure of general public is not considered since the biocidal product ACTICIDE® M 20 S is only for professional use and only professionals have access to respective premises. The secondary exposure of professionals being exposed to MIT vapours and dermal exposure from contact with paper have been addressed under the professional indirect exposure scenario.

Indirect exposure to MIT via mouthing treated paper is possible exposure scenario for children. It is assumed that dermal exposure of professionals represents the worst case scenario for exposure of general public and is considered to be covered by scenario for professionals since they are exposed to MIT residues frequently and for longer duration, in addition the area of contact with skin is higher compared to mucous area in child's mouth.

The intended use of MIT as slimicide for paper pulp (PT 12) may result in food contamination via residues in paper used for food packaging. However, the assessment of residue transfer to food is not relevant for PT 12 because exposure to MIT residues resulting from migration from food packaging material is not expected.

2.2.1. Environmental Risk Assessment

2.2.1.1. Fate and distribution in the environment

Abiotic degradation

MIT was hydrolytically stable at all tested pH levels. MIT photodegraded in water under exposure to natural sunlight at a moderate rate with half-lives of 11.1 and 18.2 days, respectively. Abiotic degradation of MIT in aqueous media occurs at a moderate rate and is significantly slower than aquatic biodegradation. Thus the primary route of dissipation in the environment is biological. The Technical Meeting TMIV08 (December 2008) agreed that identification of photodegradation products can be waived in the specific case of CMIT and

MIT, because biodegradation is faster than photodegradation. There is no need for further work to confirm the identity of photodegradation products. In the troposphere, the calculated radical catalyzed degradation of MIT and its metabolites is very rapid resulting in half-life of 16.6 hours for the parent and 31.8 hours or less for metabolites.

Biodegradation

Results from tests on ready biodegradation showed that MIT was not readily biodegradable in this test. However, due to its biocidal nature, MIT is not suitable for testing under standard ready biodegradation protocols and inhibited the microorganisms in the tests. Biodegradation simulation tests in fresh water, water-sediment and soil microcosms demonstrated that dissipation of MIT from the test systems is rapid. Dissipation half-lives at 20 ºC are <7 d for surface water, 0.87 – 4.17 days in water-sediment systems (corrected to a standard temperature of 12 ºC) and 0.15 - 0.51 days in soil (corrected to a standard temperature of 12 ºC). Dissipation consists of mineralization, primary degradation and adsorption to organic matter.
Metabolism involves cleavage of the isothiazolone ring. In a water-sediment study two major metabolites have been tentatively identified as 2-(methylcarbamoyl) ethene sulfonic acid and 2-hydroxyethane sulfonic acid. In a third study, one major degradation product was formed in both aquatic systems consisting apparently of two compounds or groups (M1 and M2), both of higher polarity than MIT. In soil, two metabolites were quantified far above 10 %: 2-(methylcarbamoyl)-ethene sulfonic acid (max 29 % of applied radioactivity) and 2-(methylcarbamoyl)-1-oxo-ethane sulfinic acid (max 21.4 % of applied radioactivity). Current data suggests that these are actually the cis and trans isomers of 2-(methylcarbamoyl)-ethene sulfonic acid. Two further transient metabolites, N-methyl-3-hydroxypropionamide and N-methyl-2-oxo-propionamide, reached 10% or more of applied activity. Another metabolite, identified as N-methyl-3-(methylcarbamoyl)-ethynylsufanyl-acrylamide, reached more than 5% of the applied activity in three consecutive samplings. MIT formed bound residues in the water-sediment and the soil studies in amounts of about 39-61.5 % of applied radioactivity in combination with 18-47% mineralisation to CO_2 at the end of the studies. The proposed identity of metabolites cannot be considered definitive as no reference structures were included in the studies or structures differed from the reference substances included in the studies. More information on transformation products is not considered necessary because the substance is shown to be degraded rapidly to transient metabolites and given what is known about the degradation pathway of isothiazolones from public literature.

Adsorption

The available studies indicate a low adsorption potential of MIT (K_{OC} 6.4-10 l/kg). In sewage treatment plants and surface waters, MIT will be predominantly present in the water phase. The substance will not accumulate in sludge or sediments. MIT may have a potential for leaching in soil, but the rapid biodegradation of the substance in soil (half-life < 0.5 day) indicates that the risk for groundwater can be considered very low.

Bioconcentration

Experimental log K_{ow} value for MIT at pH 7 and 20 ºC was -0.32. The BCFfish for MIT was estimated as 0.107 l/kg. MIT has a log K_{ow} << 3 and its potential for bioaccumulation is negligible.

Summary table on relevant physico-chemical and fate and behaviour parameter of the active substance			
	Value	**Unit**	**Remarks**
Molecular weight	115.16		
Log Octanol/water partition coefficient	-0.32	Log 10	Exp. value at standard conditions (20 ºC/pH 7)
Organic carbon/water partition coefficient (Koc)	7.5	l/kg	Arithmetic mean (AR MIT, 2014)
Henry's Law Constant (20 °C)	0.64	Pa m^3/mol	Geometric mean value from exp. studies (extrapolated)
Biodegradability	Not ready biodegradable		
Rate constant for STP	0.04	day^{-1}	Value from exp. flow-through study.
DT_{50} for biodegradation in surface water	2.21	day (at 12ºC)	Exp. geom. mean value for whole system from freshwater water/sediment systems
DT_{50} for hydrolysis in surface water	$1 \cdot 10^6$	day (at 12ºC /pH 7)	Default value in EUSES (surrogate zero)
DT_{50} for photolysis in surface water	18.1	day	Highest value from exp. studies (n=2)
DT_{50} for degradation in soil	0.51	day (at 12ºC)	Highest value from exp. studies
DT_{50} for degradation in air	16.6	hr	Atkinson calculation method

2.2.1.2. Effects assessment

Aquatic toxicity

Acute and long-term studies are available for fish, invertebrates and algae. Within trophic levels differences between toxicity to freshwater species and toxicity to saltwater species are less than a factor 10. As agreed in TMI-13 the lowest value of either the geometric mean value of the 24h $E_rC_{10,ini}$ for the freshwater species *Pseudokirchneriella subcapitata* or the single reliable 24h $E_rC_{10,ini}$ for the saltwater species *Skeletonema costatum* should be used to derive the freshwater PNEC. The two values of 0.062 mg/l and 0.024 mg/l for the freshwater species *Pseudokirchneriella subcapitata* result in a geometric mean value of 0.039 mg/l which is slightly lower than the single value of 0.044 mg/l for the saltwater species *Skeletonema costatum*. An assessment factor of 10 is applied, since NOEC/EC_{10} values are available for three trophic levels:

$PNEC_{water}$ = 0.0039 mg a.i./l or 3.9 µg a.i./l

MIT exhibits relatively low chronic toxicity to freshwater sediment-dwelling invertebrates. The physico-chemical properties of MIT ($logK_{OW}$ < 0) and its rapid degradation in surface waters (whole system DT_{50} in water-sediment systems) suggest that the active substance is not likely to partition into sediment to a significant extent. Given the negligible exposure, a PNEC for sediment organisms is not deemed to be necessary.
Moreover, although chronic sediment toxicity data are available, these test data are not required deriving $PNEc_{sed}$ as the reported concentrations are based on those measured in sediment at t_0 and MIT degrades rapidly. A $PNEC_{sed}$ derived from equilibrium partitioning is therefore more adequate. Considering that in this case the PEC/PNEC ratio for water and sediment is similar, risk assessment for fresh water covers that of sediments as well.
The $PNEC_{STP}$ was refined based on three additional OECD TG 209 (2010) studies submitted shortly after discussion in WG-IV-2016. One study concerned activated sludge from a municipal STP and two studies concerned activated sludge from an industrial STP. Following an ad hoc follow-up consultation and in addition an e-consultation, it was decided to rely on the new data and to derive the PNEC from the lowest EC_{10} of 4.13 mg/L and a standard assessment factor of 10 (see summary WG-IV-2016 Ad-hoc follow-up: Item 6.3 - MIT PT 12).

$PNEC_{STP}$ = 0.41 mg a.i./l

Terrestrial toxicity

Short-term toxicity studies are available with earthworms, soil microorganisms and plants. MIT degrades very fast in soil, resulting in a short-term exposure. The $PNEC_{soil}$ is calculated with an assessment factor of 1000 on the lowest EC_{50} of 18 mg a.i./kg dry soil from the plant tests. A factor of 1.13 is applied to correct from dry weight to wet weight. This conversion is based on a standard soil which is defined as a soil with an organic matter content of 3.4%:

$PNEC_{soil}$ = [18/1.13 x (0.034/0.013)] / 1000 = 0.0417 mg/kg (wet wt)

Summary table on calculated PNEC values	
Compartment	**PNEC**
Freshwater	0.0039 mg a.i./l or 3.39 µg a.i./l
STP	0.41 mg a.i./l*
Soil	0.0417 mg/kg (wet wt)

* Refined based on additional data (see above)

2.2.1.3. Exposure assessment and risk characterisation

Summary table on compartments exposed and assessed: scenario paper mill without connection to a pulp mill		
Compartment	**Exposed (Y/N)**	**Assessed (Y/N)**
Freshwater	Y	Y
Sediment	N	N
STP	N	N

Air	N	N
Soil	N	N
Groundwater	N	N

Summary table on compartments exposed and assessed: scenario paper mill with connection to a pulp mill		
Compartment	**Exposed (Y/N)**	**Assessed (Y/N)**
Freshwater	Y	Y
Sediment	N	N
STP	Y	Y
Air	Y	N
Soil	Y	Y
Groundwater	Y	Y

The exposure assessment and risk characterisation was performed for two scenarios: the scenario paper mill without connection to a pulp mill and the scenario paper mill with connection to a pulp mill.

In the scenario paper mill without connection to a pulp mill, the wastewater after settling is treated only by mechanical and chemical means in the paper mill. As for the settling, the degradation of slimicide is taken into account to estimate the concentration of the substance in the effluent of the paper mill. Then this effluent is discharged directly to surface water where a predicted environmental concentration of MIT in freshwater was estimated assuming a dilution.

In the scenario paper mill with connection to a pulp mill, the wastewater after settling is discharged to an industrial STP and afterwards into fresh surface waters from the STP. An emission to a STP is estimated in taking into account the effluent discharge rate of a paper mill (5000 $m^3.day^{-1}$).

The active ingredient was considered to be stable to hydrolysis. The rate constant used for biodegradation during settling and mechanical/chemical treatment derives from the biodegradation in freshwater study as a worst case (AR MIT, 2014).

A tiered approach has been considered when the releases were directed to the STP. In Tier 1, 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 (0.122 in the effluent and 0.0664 in the sludge). In Tier 2, the fractions of emission directed to water by the STP, to sludge by the STP and the fraction degraded in the STP were extrapolated from the SimpleTreat model considering the rapid biodegradation of the active substance (0.167 in the effluent, 0.0007 in the sludge and 0.832 degraded).

The standard dilution factor for waste water entering surface water is defined from a default river flow rate of 18 000 $m^3.day^{-1}$ (0.2 $m^3.s^{-1}$) and from a default effluent discharge rate of 2000 $m^3.day^{-1}$ (municipal STP) as (18000+2000)/2000 = 10. However the default effluent discharge rate of a paper plant is 5000 $m^3.day^{-1}$ (for the scenario paper mill without connection to a pulp mill) corresponding to a dilution factor of 5

((18000+5000)/5000)). It can be considered that a flow rate of 18 000 $m^3.day^{-1}$ corresponds to a very low flow rate. Large paper plants are unlikely to be located on small waterways.

Consequently the dilution factor was adapted to take into account the various types of water bodies in Europe (canals, rivers, large rivers) and the temporal and seasonal variations of flow rates. In the WGII-2014 ENV discussion for C(M)IT-MIT[1] in PT12 it was agreed that refined values like agreed for PT11 can in addition be used for PT12 as well. Refined calculations of concentrations in surface water were done for a limited river with a river flow rate of 54 000 $m^3.day^{-1}$ (dilution factor 10), a moderate sized river with a river flow rate of 400 000 $m^3.day^{-1}$ (dilution factor 200) and a medium/large river with a river flow rate of 2 000 000 $m^3.day^{-1}$ (dilution factor 1000).

1 Final minutes of WGII-2014_ENV_6.4 Draft CAR on C(M)IT/MIT (PT 2,4,6,11,12,13)

Exposure assessment

Summary table on calculated PEC values					
	PEC_{STP}	**PEC_{water}**	**PEC_{soil} agricultural soil**	**PEC_{GW} pore water**	**PEC_{air}**
	[mg/m^3]	[mg/l]	[mg/m^3]	[µg/l]	[mg/m^3]
Scenario paper mill without connection to a pulp mill	n.a.	1.35 (DILUTION 10) $6.75 \cdot 10^{-2}$ (DILUTION 200) $1.35 \cdot 10^{-2}$ (DILUTION 1000)	n.a.	n.a.	n.a.
Scenario paper mill with connection to a pulp mill Tier 1	0.494	$4.94 \cdot 10^{-2}$ (DILUTION 10) $2.47 \cdot 10^{-3}$ (DILUTION 200) $4.94 \cdot 10^{-4}$ (DILUTION 1000)	1.00	0.0163 *	Negligible
Scenario paper mill with connection to a pulp mill Tier 2	0.676	0.0676 (DILUTION 10) $3.38 \cdot 10^{-3}$ (DILUTION 200) $6.76 \cdot 10^{-4}$ (DILUTION 1000)	$1.05 \cdot 10^{-2}$	$1.72 \cdot 10^{-4}$ *	Negligible

* Estimates are very conservative as it does not take into account the very rapid degradation of MIT in soil. The actual risk of exceedance of the limit of 0.1 µg/l via sludge application once a year can be considered low for MIT.

Risk characterization

Summary table on calculated PEC/PNEC values			
	PEC/PNEC$_{STP}$	**PEC/PNEC$_{water}$**	**PEC/PNEC$_{soil}$**
Scenario paper mill without connection to a pulp mill – Limited river (dilution factor 10)	n.a.	**346**	n.a.
Scenario paper mill without connection to a pulp mill – Moderate sized river (dilution factor 200)		**17.3**	
Scenario paper mill without connection to a pulp mill – Medium/large river (dilution factor 1000)		**3.46**	
Scenario paper mill with connection to a pulp mill Tier 1 – Small river (dilution factor 5)	**1.2**	**25.3**	**24.0**
Scenario paper mill with connection to a pulp mill Tier 1 – Limited river (dilution factor 10)		**12.7**	
Scenario paper mill with connection to a pulp mill Tier 1 – Moderate sized river (dilution factor 200)		0.561	
Scenario paper mill with connection to a pulp mill Tier 1 – Medium/large river (dilution factor 1000)		0.127	
Scenario paper mill with connection to a pulp mill Tier 2 – Limited river (dilution factor 10)	**1.6**	**17.3**	0.25
Scenario paper mill with connection to a pulp mill Tier 2 – Moderate sized river (dilution factor 200)		0.87	
Scenario paper mill with connection to a pulp mill Tier 2 – Medium/large river (dilution factor 1000)		0.173	

Conclusion

For the **Scenario paper mill without connection to a pulp mill** refined calculations result in a ratio $PEC_{water}/PNEC_{water}$ >1 calculated from the proposed of ACTICIDE® M 20 S as slimicide in paper mill at 15 ppm indicating unacceptable risk to the water compartment for this scenario with direct drainage of waste water from the paper mill to surface water. Both in **Tier 1** and in **Tier 2** for the **Scenario paper mill with connection to a pulp mill**, the $PEC_{STP}/PNEC_{STP}$ value calculated from the proposed uses of ACTICIDE® M 20 S as slimicide in paper mill at the claimed continuous dose of 15 mg a.i./l is slightly > 1, indicating unacceptable risk to microorganisms in the industrial on-site STP. This risk can be mitigated by various RMMs to reduce exposure of microorganism in the STP to MIT. These could include (but should not be restricted to) the following operational and technical control measures:

i. measurement of MIT concentration in the waste water (to be compared with the PNEC) or/and performing a test on the total toxicity of the waste water before a biological treatment at the STP;
ii. increase the minimum retention time to 8 hours for a primary settling and/or introduce chemical/mechanical treatment before biological treatment at the STP;
iii. addition of different agents (e.g. reducing agent and/or flocculation agents) to reduce the amount MIT content during a chemical/mechanical treatment;
iv. use of collecting tanks to store waste water in case large amounts of waste water with higher MIT concentration occur, e.g. in case of system cleaning or maintenance work.

Independent from the above mentioned RMMs it is recommended to regularly control the biological treatment plant and the active biomass and if relevant, adjust the nutrition supply (nitrogen and phosphorus) to the actual need of the active biomass to maintain a sufficient amount and growth of microorganisms.

The risk to the water compartment is acceptable in case of direct discharge of waste water to a moderate or medium large river (dilution factor 200 and 1000, respectively), but not acceptable with direct discharge of waste water to a limited river (dilution factor 10). Exposure of soil, groundwater and air is considered not relevant in the **Scenario paper mill without connection to a pulp mill**. For the **Scenario paper mill with connection to a pulp mill** exposure of soil is possible via sludge application, but given the very rapid degradation of the active substance in soil the risk of leaching to groundwater can be considered low for MIT. The more realistic Tier 2 calculation results in a ratio $PEC_{soil}/PNEC_{soil}$ <1 calculated from the proposed of ACTICIDE® M 20 S as slimicide in paper mill at 15 ppm indicating acceptable risk to soil organisms.

2.2.1.4. PBT and POP assessment

MIT does not fulfil the PBT/vPvB criteria and can therefore not be considered a PBT/vPvB substance. It does not fulfil the T-criterion based on the lowest aquatic NOEC/EC_{10} of 0.024 mg/l i.e. not <0.01 mg/l. It also does not meet the trigger value for BCF > 2000 for B or > 5000 for vB. Regarding persistency MIT rapidly biodegrades primarily in aquatic simulation tests with a half-life in the range of 0.87 - 4.17 days in surface water at 12 °C. None of the major metabolites can be considered persistent. The criterion for substance to be persistent in soil is T ½ >120 days, while experimental values for MIT are < 1 day. MIT does therefore not fulfil the P/vP-criterion.

2.2.2. Assessment of endocrine disruptor properties

The endocrine disrupting effects cannot be determined at present as the criteria are not yet agreed. However, in the absence of significant effects on endocrine organs and/or reproduction in standard mammalian toxicity studies it has been concluded that MIT does not have endocrine-disrupting properties in mammals. In view of this it is reasonable to assume that in mammalian wildlife and companion animals at least, endocrine disruption is not a concern.

2.3. OVERALL CONCLUSIONS

The outcome of the assessment for MIT product-type 12 is specified in the BPC opinion following discussions at the 19. meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA web-site.

2.3.1. Requirement for further information

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal for the approval of MIT.

2.4. LIST OF ENDPOINTS

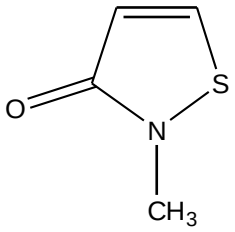
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List of endpoints

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Common Name)	No ISO name accepted or proposed. Names commonly used: 2-methyl-2H-isothiazol-3-one, MIT, Methylisothiazolinone, 2-methyl-4-isothiazoline-3-one.
Product-type	PT 12: Slimicides

Identity

Chemical name (IUPAC)	2-methylisothiazol-3(2H)-one
Chemical name (CA)	2-methyl-3(2H)-isothiazolone (9CI CAS), 2-methyl-4-isothiazolin-3-one (7CI & 8CI CAS name)
CAS No	2682-20-4
EINECS No	220-239-6
Other substance No.	ENCS N° 5-5235
Minimum purity of the active substance as manufactured (g/kg or g/l)	Thor GmbH: > 950 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	5-chloro-2-methyl-2H-isothiazol-3-one (C(M)IT): < 1 g/kg (dry matter), no additives
Molecular formula	C_4H_5NOS
Molecular mass	115.16 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	*Rohm and Haas:* 46.7 - 48.3 °C (purity = 99.7 %)	*Thor GmbH:* 39 – 42.8 °C (purity = 95.5 %.)
Boiling point (state purity)	*Rohm and Haas:* The active substance does not boil prior to decomposition (purity > 95 %).	*Thor GmbH:* The active substance does not boil prior to decomposition (purity > 99 %).

Temperature of decomposition	*Rohm and Haas:* Decomposition starts at 235 °C (purity > 95 %).	*Thor GmbH:* Decomposition at about 236 °C (purity > 99 %).
Appearance (state purity)	*Rohm and Haas:* Off-white to light brown solid at 20 °C (purity = 99.7 %, purified a.i.; purity = 98.71 %, technical grade a.i.)	*Thor GmbH:* Light-yellow crystalline solid, mild odour (> 95 %)
Relative density (state purity)	*Rohm and Haas:* 1.35×10^3 at 25 °C (purity > 95 %)	*Thor GmbH:* 1.39×10^3 at 20 °C (purity > 99 %)
Surface tension	*Rohm and Haas:* 68.8 mN/m at 19.5 ºC	*Thor GmbH:* 72.32 mN/m at 20 º C
Vapour pressure (in Pa, state temperature)	*Rohm and Haas:* 0.73 Pa at 25 ºC (extrapolated) 0.408 Pa 20 ºC (extrapolated)	*Thor GmbH:* 1.60 Pa at 25 °C (extrapolated) 0.99 Pa at 20 °C (extrapolated)
	Geometric mean: 0.64 Pa at 20 °C (n=2)	
Henry's law constant (Pa m^3 mol^{-1})	*Rohm and Haas:* $< 8.19 \times 10^{-5}$ $Pa \cdot m^3 \cdot mol^{-1}$ at 20 ºC and pH 5	*Thor GmbH:* $< 4.39 \times 10^{-5}$ $Pa \cdot m^3 \cdot mol^{-1}$
Solubility in water (g/l or mg/l, state temperature)	*Rohm and Haas:* pH 5, 9:> 1000 g/l at 20 °C	*Thor GmbH:* pH 5, 7, 9: > 1000 g/l at 10, 20 and 30 °C pH 4.5:> 4287.2 g/l at 20 °C
Solubility in organic solvents (in g/l or mg/l, state temperature)	*Rohm and Haas:* <u>Solubility in hexane:</u> 2.42 g/l at 30 ºC 0.93 g/l at 10 ºC <u>Solubility in ethyl acetate:</u> > 1000 g/l at 30 ºC 562.15 g/l at 10 ºC	*Thor GmbH:* 1.46 g/l in <u>n-hexane</u> at 21 °C 143.6 g/l in <u>xylene</u> at 21 °C
Stability in organic solvents used in biocidal products including relevant breakdown products	Not applicable; active substance as manufactured does not include an organic solvent.	

Partition coefficient (log P_{OW}) (state temperature)	Rohm and Haas: log P_{ow} = - 0.486 at 24 °C, pH not stated (not pH and T dependent)	*Thor GmbH:* pH 5: log P_{ow} = -0.26 at 20 °C pH 7: log P_{ow} = -0.34 at 10 °C pH 7: log P_{ow} = -0.32 at 20 °C pH 7: log P_{ow} = -0.34 at 30 °C pH 9: log P_{ow} = -0.28 at 20 °C
Hydrolytic stability (DT_{50}) (state pH and temperature)	*Rohm and Haas:* 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 720 hours.	*Thor GmbH:* pH 4, 7 and 9: DT_{50} >1 year (extrapolated from results of a preliminary test at 50 °C)
Dissociation constant	*Rohm and Haas:* Not applicable; MIT does not dissociate into ionic species. (Expert statement)	*Thor GmbH:* Low dissociated compound pK > 2.81 (purity = 98.5 %; conductometer method)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	*Rohm and Haas:* Neutral pH: λ_{max} at 274 nm, Abs. = 0.93203, ∈ = 7760 Acid pH: λ_{max} at 266 nm, Abs. = 0.94372, ∈ = 7950 Acid pH: λ_{max} at 212 nm, Abs. = 0.33744, ∈ = 2843 Basic pH: λ_{max} at 274 nm, Abs. = 0.93627, ∈ = 8085 Basic pH: λ_{max} at 215 nm, Abs. = 0.20294, ∈ = 1752	*Thor GmbH:* Neutral pH: λ_{max} at 273 nm, log ε = 3.88 Acid pH: λ_{max} at 273 nm, log ε = 3.88 Methanol: λ_{max} at 277 nm, log ε = 3.87
Photostability (DT_{50}) (aqueous, sunlight, state pH)	DT_{50} = 11.1 -18.2 d at pH 7 (sunlight), geometric mean 14.2 d	
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not determined.	
Flammability	*Rohm and Haas:* Not highly flammable	*Thor GmbH:* Not flammable
Explosive properties	Not explosive	
Oxidising properties	Not oxidising	

Classification and proposed labelling**

with regard to physical/chemical data	-

with regard to toxicological data	**Hazard Class and Catagory**	**Hazard Statement**
	Acute Tox. 3 (oral) Acute Tox. 3 (dermal) Acute Tox. 2 (inhalation) Skin corr. 1B Skin sens. 1A	H301; Toxic if swallowed. H311; Toxic in contact with skin. H314; Causes severe skin burns and eye damage. H317; May cause an allergic skin reaction. H330; Fatal if inhaled.
with regard to fate and behaviour data	-	
with regard to ecotoxicological data	**Hazard Class and Category**	**Hazard Statement**
	Aquatic Acute 1 Aquatic Chronic 1	H400; Very toxic to aquatic life H410; Very toxic to aquatic organisms with long lasting effects

Supplementary hazard statement: EUH071 Corrosive to the respiratory tract.

** Classification and labelling of MIT was amended according to the proposal of RAC on March 10, 2016.

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	*Rohm and Haas:* Reversed Phase High Performance Liquid Chromatography with UV detection (254 nm).	*Thor GmbH:* Reversed Phase High Performance Liquid Chromatography with UV detection (275 nm). Technical active substance is 50 % aqueous solution.
Impurities in technical active substance (principle of method)	CONFIDENTIAL INFORMATION included in the Confidential part of the dossier.	

Analytical methods for residues

Soil (principle of method and LOQ)	*Rohm and Haas:* Solid phase extraction followed by reversed phase HPLC with UV	*Thor GmbH:* Not submitted; an active substance will not be present in soil due to high mobility and fast

	detection (275 nm); LOQ = 0.05 µg/g of soil or sediment.	degradation rate.
Air (principle of method and LOQ)	*Rohm and Haas:* Trap airborne MIT on silica gel, extract and analyze by HPLC/MS/MS; LOQ = 150 µg/m^3.	*Thor GmbH:* Extraction followed by HPLC with UV detection; LOQ = 0.26 µg/m^3 in air
Water (principle of method and LOQ)	*Rohm and Haas:* Reversed Phase High Performance Liquid Chromatography with MS/MS detection; LOQ = 0.05 µg/l (drinking water, surface water, sea water)	*Thor GmbH:* HPLC/MS/MS; LOQ (limit of quantification) = 0.1 µg/l (surface water)
Body fluids and tissues (principle of method and LOQ)	-	
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	*Rohm and Haas:* Extraction/dilution followed by HPLC/MS/MS analysis; Limit of detection is 0.004 mg/l ppb).	*Thor GmbH:* HPLC-MS analysis; LOQ (limit of quantification) = 0.025 µg/ml LOD (limit of detection) =0.006 µg/ml The available analytical method is suitable for the determination of MIT in the food simulants acetic acid, 10 % ethanol and olive oil.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required.	

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	*Rohm and Haas:* **53**-69 **%** at 50 mg base-eq./kg b.w. 67-73 % at 5 mg base-eq./kg b.w. (rat)	*Thor GmbH:* 67-69 % at 50 mg base-eq./kg b.w. (rat)
Rate and extent of dermal absorption:	*Rohm and Haas:* *In vitro* rat skin: 68-81 % over the range of concentrations tested (25 to 150 ppm MIT). *In vitro* human skin: 66, 62 and 67 % from an aqueous solution of MIT at concentrations of 52.2, 104 and 313 µg MIT/ml, respectively.	
	100 % for the active substance and biocidal product 67% for an aqueous solutions **75 % default value, based on EFSA guidance on dermal absorption (2012) for ≤ 5 % a.s.**	
Distribution:	*Rohm and Haas, Thor GmbH:* Widely distributed; higher values than average were detected in the blood.	
Potential for accumulation:	*Rohm and Haas, Thor GmbH:* No evidence of accumulation in the animal body.	
Rate and extent of excretion:	*Rohm and Haas, Thor GmbH:* Rapidly and extensively eliminated.	
Toxicologically significant metabolite	*Rohm and Haas, Thor GmbH:* None of the metabolites are considered to be of concern.	

Acute toxicity

LD_{50} oral	*Rohm and Haas:* 120-235 mg/kg b.w. (rat) 167 mg/kg b.w (mouse)	*Thor GmbH:* 328 mg/kg b.w. (rat)
LD_{50} dermal	*Rohm and Haas:* 242 mg/kg b.w. (rat)	*Thor GmbH:* >2000 mg/kg bw
LC_{50} inhalation	*Rohm and Haas:* 0.11 mg a.i./l air, 4-hours, nose-only (rat)	*Thor GmbH:* 0.134 mg a.i./l air, 4-hours, nose-only (rat)
Skin irritation	*Rohm and Haas:* Corrosive; 0.5 ml of MIT applied undiluted. (rabbit) Corrosive; 51.5 % MIT for	*Thor GmbH:* Corrosive; 0.5 ml of MIT applied undiluted (rabbit)

	60 min. (human epidermal construct); non-corrosive after 3 min. 1.7 % non-corrosive (3 and 60 min). 21-day cumulative skin irritation (humans): not irritant ≤ 500 ppm (39.5 μg/cm^2)	
Eye irritation	*Rohm and Haas:* Corrosive by analogy to skin irritation corrosive results.	*Thor GmbH:* Corrosive by analogy to skin irritation corrosive results.
Airway irritation	*Rohm and Haas:* RD_{50} > 157 µg /l air (mouse)	*Thor GmbH:* RD_{50} > 157 µg /l air (mouse)
Skin sensitization (test method used and result)	*Rohm and Haas:* Sensitizer SCL for skin sensitization ≥0.0015%*	*Thor GmbH:* Sensitizer

* The SCL for MIT was amended according to the proposal of RAC, March 10, 2016.

Acute toxicity of MIT metabolites

LD_{50} oral, N-(methyl) malonamic acid (NMMA)	*Rohm and Haas:* 3550 mg NMMA/kg b.w. (rat)	*Thor GmbH:* /
Skin sensitization (test method used and result), N-Methyl malonamic acid (NMMA)	*Rohm and Haas:* Local lymph node assay: not a sensitizer at concentrations up to and including 300,000 ppm NMMA [6000 µg NMMA/cm^2] (mouse)	*Thor GmbH:* /

Repeated dose toxicity

Species/ target / critical effect	Rat-dog-rabbit/reduced food and/or water consumption, reduced body weight gain, increased spleen weight	
Lowest relevant oral NOAEL / LOAEL	*Rohm and Haas:* NOAEL = **9.9** and 11.1 mg a.i./kg bw/day in males and females, respectively (400 ppm); 3 months (dog, diet). LOAEL = 40.6 and 40.9	*Thor GmbH:* NOAEL = 30 mg a.i./kg bw/day; 3 months (rat, gavage). LOAEL not determined.

	mg/kg bw/day (1500 ppm), based on transient decreased body weight gain and food consumption	
Lowest relevant dermal NOAEL / LOAEL	*Rohm and Haas:* Test with CMIT/MIT (3:1): 90 days NOAEL (rabbit) was not determined; LOAEL = 0.1 mg CMIT/MIT/kg bw/day (100 ppm); irritation at site of contact 30 months NOEL (mouse) = 400 ppm CMIT/MIT (3:1). There were no systemic toxic effects in this study.	
Lowest relevant inhalation NOAEL / LOAEL	*Rohm and Haas, Thor GmbH:* Test with CMIT/MIT (3:1): 90 days NOEL (rat) = **0.34 mg CMIT/MIT (3:1)/m³** based on irritation to the respiratory tract. 90 days LOEL (rat) = 1.15 mg CMIT/MIT (3:1)/m^3, based on slight, treatment-related rhinitis. There were no systemic toxic effects in this study.	

Repeated dose toxicity of MIT metabolites

Species/ target / critical effect	Rat/-	
Lowest relevant oral NOAEL / LOAEL	*Rohm and Haas:* N-methyl malonamic acid (NMMA): 90 days NOEL (diet, rat) = 13-15 mg NMMA/kg bw/day (100-220 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.	*Thor GmbH:* /

Genotoxicity	*Rohm and Haas:* Genotoxicity *in vitro:* negative in Ames test (with and without S9) and in gene mutation assay in CHO cells (HGPRT). Negative in chromosome aberration assay in CHO cells. Genotoxicity *in vivo:* negative in micronucleus assay in	*Thor GmbH:* Genotoxicity *in vitro:* negative in Ames tests (with and without S9) and in gene mutation assay in CHO cells (HGPRT). Negative in chromosomal aberration assay in human lymphocyte culture. Genotoxicity *in vivo:* negative in micronucleus assay in mouse bone

	mouse bone marrow and in UDS assay in rat hepatocytes.	marrow.

Genotoxicity of MIT metabolites

Rohm and Haas: N-methyl malonamic acid (NMMA): negative in Ames test, with and without S9.	*Thor GmbH:* /

Carcinogenicity

Species/type of tumour	*Rohm and Haas:* Carcinogenicity study performed with CMIT/MIT (3:1): No evidence of carcinogenicity after oral administration (rat, 24 months) and dermal administration (mouse, 30 months). MIT is considered not carcinogenic.	*Thor GmbH:* Carcinogenicity study performed with CMIT/MIT (3:1): No evidence of carcinogenicity after oral administration (rat, 24 months). MIT is considered not carcinogenic.
Lowest dose with tumours	/	

Reproductive toxicity

Species/ Reproduction target / critical effect	No effects on reproduction in rats. Reduced body weight gain in parents and offspring, reduced food intake.	
Lowest relevant reproductive NOAEL / LOAEL	*Rohm and Haas, Thor GmbH:* Maternal and foetal (rat): NOAEL = 15-19 mg MIT/kg/day (male, rat) [200 ppm] NOAEL = 22-26 mg MIT/kg/day (female, rat) [200 ppm]	
Species/Developmental target / critical effect	Not teratogenic in rats and rabbits.	
Developmental toxicity		
Lowest relevant developmental NOAEL / LOAEL	*Rohm and Haas:* NOAEL = 30 mg/kg/day (foetal, rabbit) NOAEL = 10 mg/kg/day (maternal, rabbit)	*Thor GmbH:* NOAEL = 30 mg/kg/day (foetal, rabbit) NOAEL = 10 mg/kg/day (maternal, rabbit)

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	No evidence of neurotoxicity in multiple dose studies.
Lowest relevant developmental NOAEL / LOAEL	No evidence of neurotoxicity in multiple dose studies.

Other toxicological studies

Rohm and Haas, Thor GmbH:

MIT was tested in clinical irritation and sensitisation trials in the United States.

Thresholds for skin sensitization have been established to be at or near 1000 ppm a.i. in water, no cumulative skin irritation was observed after 21 consecutive days of exposure up to and including 500 ppm MIT **.**

Rohm and Haas :

MIT was not a skin sensitizer in humans at concentrations up to and including 600 ppm (30 $\mu g/cm^2$).

Medical data

Rohm and Haas:

One incidental exposure to MIT was reported from one MIT production plant. Besides that, no reports on skin or other problems were reported.

Summary	Value	Study	Safety factor
ADI (if residues in food or feed)	0.05 mg/kg bw/d	90-days dietary study (dog)	200
Systemic AEL (acute and medium -term)	0.053 mg/kg bw/day	90-days dietary study (dog)	100 (53 % oral absorption)
Systemic AEL (long term*)	0.027 mg/kg bw/day	90-days dietary study (dog)	200 (53 % oral absorption)
Inhalation AEC (acute, medium)	0.043 mg/m^3	90-days inhalation study with CMIT/MIT (3:1 in rat	8
Inhalation AEC (long-term)	0.021 mg/m^3	90-days inhalation study with CMIT/MIT	16

		(3:1 in rat	
Dermal NOAEC	0.0015 % (15 ppm)**	Animal data and human observations	N/A
Drinking water limit	Not required.	N/A	N/A
ARfD (acute reference dose)	0.10 mg/kg bw/day	Rabbit developmental study	100

* There is no chronic study upon which a long term AEL can be based, due to a well documented waving proposal. However, as local irritation is dominating and potential adverse systemic effects seems to occur at higher doses, the RMS proposes that the AEL long term is set at the same level as the AEL medium term (0.027 mg/kg bw/day).

** Dermal NOAEC for MIT was amended according to the proposal of RAC on March 10, 2016.

Acceptable exposure scenarios (including method of calculation)

Professional users

PT12
The representative biocidal product ACTICIDE® M 20 S (20 % MIT) for use in product type 12 as a slimicide for preservation in paper mills against harmful microorganisms in end concentration of 15 mg a.s./l applied by shock or continuous dosing was evaluated.

Operator's exposure assessment for this product type includes primary exposure from loading the biocidal product into the cooling system, and post-application tasks (sampling process liquid (dip slide), maintenance of process equipment, cleaning dispensing pumps and empty containers). Secondary exposure during inhalation of MIT residue in air and exposure through contact with MIT residues in paper were also estimated.

Exposure assessment is based on simple database models listed below:

	Relevant model
Mixing and loading phase – Automated loading:	RISKOFDERM Toolkit Connecting lines
Post application phase: - sampling process liquid (dip slide) - maintenance of process equipment - cleaning dispensing pumps and empty containers	BEAT database (2008) 'Cleaning of spray equipment'
Secondary exposure: Inhalation of spray from preserved cooling water	TnsG Part 2 June 2002, Spraying model 1

	Dermal exposure through contact with paper	Reverse reference approach
	PPE: Appropriate risk mitigation measures must be applied during different phases of use of the ACTICIDE® M 20 S (20 % MIT) in order to prevent any spillage on skin. Besides the technical and organizational RMM adequate for high hazard chemicals, appropriate PPE must be used during automated loading (impermeable coverall, protective gloves and face shield), sampling process liquid, maintenance of processing equipment and cleaning of pumps and empty drums (impermeable coverall, protective gloves and face shield).	
Non-professional users	Non-professional use is not envisaged.	
Indirect exposure as a result of use	Inhalation of spray from preserved paper pulp and skin contact with treated paper do not pose an unacceptable risk for general public. Both exposure scenarios of general public are covered by risk assessment for indirect professional exposure.	

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	*Rohm and Haas:* pH 5, 7, and 9: DT_{50} >>30 d at 24 °C	*Thor GmbH:* pH 4, 7 and 9: DT_{50} >1 year (extrapolated from results of a preliminary test at 50°C)
	No data on hydrolysis of relevant metabolites available	
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	*Rohm and Haas:* DT_{50} = 11.1 d at pH 7 (sunlight) Major metabolites: 3-methyl-4-thiazolin-3-one (max. 40 %) and N-methyl malonamic acid (max. ≤ 39 %)	*Thor GmbH:* DT_{50} = **18.2 d** at pH 7 (sunlight) No conclusive identification of major metabolites
	No data on photolysis of relevant metabolites available	
Readily biodegradable (yes/no)	*Rohm and Haas:* No 48-56% biodegradation in Modified Sturm Test Ready biodegradation	*Thor GmbH:* No 0 % biodegradation in Closed Bottle Test

	tests with metabolites N-methyl malonamic acid: Yes N-methyl acetamide: Yes Malonamic acid: Yes	
Biodegradation in freshwater	-	*Thor GmbH:* Rapid biodegradation, DT_{50} <7 d at 20 °C
Biodegradation in estuarine water	*Rohm and Haas:* DT_{50} = 1.25-1.38 d at 20 °C DT_{50} = 2.38-2.63 d at 12°C DT_{50} = 3.03-3.34 d at 9 °C	-
Biodegradation in marine water	-	*Thor GmbH* DT_{50} = 3.6 d at 20 °C DT_{50} = 5.7 d at 9 °C
Biodegradation in STP	*Rohm and Haas:* DT_{50} = 0.04 d at 20 °C DT_{50} based on mineralization at 20 °C: 1.67 d	-
Aerobic degradation in freshwater water/sediment systems	*Rohm and Haas:* Whole system DT_{50}: 0.46-1.4 d at 20 °C (n=2) (0.86-1.7 d at 12 ºC)	*Thor GmbH:* Whole system DT_{50}: 1.28-2.20 d at 20 °C (n=2) (3.43-4.17 d at 12 ºC)
	Geometric mean DT_{50} (12°C, aerobic) 2.21 d (n=5)	
Non-extractable residues	*Rohm and Haas:* Sediment bound residues reached maxima in the range of 59.4-61.5 % in various water-sediment systems. In most cases the largest fraction of non-extractable activity remained in the unextractable inorganic humin fraction.	
Distribution in water / sediment systems (active substance)	MIT remains mainly in aqueous phase. One study showed that about half of the radioactivity that could be extracted with 0.25N HCl from the sediment bound residue fraction consisted of parent compound.	

Distribution in water / sediment systems (metabolites)	Major metabolites with higher polarity than parent and low molecular weight. Metabolites remain mostly in the water phase.

Route and rate of degradation in soil

Mineralization (aerobic)	*Rohm and Haas:* Maximum of 46.6 % after 100 days (end of incubation)	*Thor GmbH:* Maximum of 25 % after 51 days (end of incubation)
Laboratory studies (range or median, with number of measurements)	*Rohm and Haas:* DT_{50lab} (20 ºC, aerobic) = 0.27 d (single first order)	*Thor GmbH:* DT_{50lab} (20 ºC, aerobic) = 0.08 d (single first order)
	DT_{50lab} (12 °C, aerobic) 0.15-0.51 d (n=2)	
	DT_{90lab} (20 °C, aerobic): not available	
	DT_{50lab} (10 °C, aerobic): not available	
	DT_{50lab} (20 °C, anaerobic): not available	
	degradation in the saturated zone: not applicable	
Field studies (state location, range or median with number of measurements)	DT_{50f}: not available	
	DT_{90f}: not available	
Anaerobic degradation	Not available	
Soil photolysis	Not available	
Non-extractable residues	*Rohm and Haas:* The % of applied ^{14}C-activity that becomes incorporated into the bound residues increased from 6.2 % to 39.7 % after 30 days of incubation and 38.8 % after 100 days of incubation. Acid hydrolysis extracted over 50 % of the activity (7.9 to 23.5 % of the applied activity). NaOH extraction showed that most of the remaining activity was associated with the fulvic acid fraction. The humin fraction contained 7.4 % of the	*Thor GmbH:* Bound residues increased from 33 % after a few hours to 55.3 % after 28 days. No acceptable mass balance maintained after first day of incubation

	applied activity after 30 days of incubation.	
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	*Rohm and Haas:* CO_2: 0-46.6 %, maximum after 100 days M3: 1.2-29.0 %, maximum after 22 hours M4: 0.5-21.4 %, maximum after 22 hours	*Thor GmbH:* No acceptable mass balance after first day of incubation
Soil accumulation and plateau concentration	No accumulation of MIT in soil as a result of quick biodegradation.	

Adsorption/desorption

Ka , Kd	*Rohm and Haas:* K_{ads} in sludge = 20.11 - 56.82 l/kg K_{ads} in soil = 0.03 - 1.07 l/kg K_{des} in soil = 0.67 - 0.96 l/kg	*Thor GmbH:*
Ka_{oc} , Kd_{oc}	$Kads_{oc}$ in soil (batch equilibrium method) Sandy loam: 7.7 l/kg Clay loam: 6.9 l/kg Silty clay loam: 6.7 l/kg Sand: 10 l/kg Loam: 6.4 l/kg $Kdes_{oc}$ in soil = 5.7 - 246.7 l/kg	$Kads_{oc}$ in soil = 2.9×10^{-25} l/kg (HPLC method)
	Aritmetric mean $Kads_{oc}$ 7.5 l/kg (n=5)	
pH dependence (yes / no) (if yes type of dependence)	Not expected.	

Fate and behaviour in air

Direct photolysis in air	*Rohm and Haas:* The phototransformation rate constant and half-life were calculated using structure activity relationship (SAR) methods. The rate constant, k, was	*Thor GmbH:* The rate constant for phototransformation of MIT in air was estimated using the AOPWIN QSAR software. A tropospheric half-life of 0.6 days (14.3

	calculated from the OH and NO_3 radical reaction processes and the resulting rate constant used to calculate the half-life. The calculated phototransformation half-life of MIT in air is 16.6 hours. For the observed metabolites and degradates, the half-live range from 25.2 to 31.8 hours.	hours) was calculated for reaction of OH-radicals with MIT, assuming 24 hours of sunlight, 25°C, and an OH-radical concentration of $5 \cdot 10^5$ cm^{-3}. The reaction with ozone was estimated to be slow as compared to the reaction with OH-radicals, half-life 6.6 days.
	For the reaction with OH-radicals $kdeg_{air}$ = $1.00 \cdot 10^{-2}$/day according to Eq. 28 (TGD), corresponding to a half-life of 10 days	
Quantum yield of direct photolysis	Not available	
Photo-oxidative degradation in air	Latitude:- N/A....Season:- N/A.... DT_{50}: N/A....	
Volatilization	Low potential due to low vapour pressure and low Henry's law constant.	

Monitoring data, if available

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
Air (indicate location and type of study)	Not available

Chapter 5: Effects on Non-target Species

Toxicity data of MIT for aquatic species

Acute toxicity to freshwater fish	*Rohm and Haas: Oncorhynchus mykiss* 96 hr LC50 4.77 mg/l(mm) 96 hr NOEC 2.01 mg/l(mm)	*Thor GmbH: Oncorhynchus mykiss* 96 hr LC50 5.71 mg/l (mm) 96 hr NOEC 3.06 mg/l(mm)
Early Life Stage toxicity to freshwater fish	*Rohm and Haas: Oncorhynchus mykiss* 98 d NOEC 4.93 mg/l(mm) egg hatch, survival 98 d NOEC 2.38	*Thor GmbH: Pimephales promelas* 33 d NOEC 2.1 mg/l (mm, survival)

	mg/l(mm) growth	
Acute toxicity to marine fish	*Rohm and Haas: Cyprinodon variegatus* 96 hr LC50 25.1 mg/l(mm) 96 hr NOEC 12.7 mg/l(mm)	-
Acute toxicity to freshwater invertebrates	*Rohm and Haas: Daphnia magna* 48 hr EC_{50} 0.998 mg/l(mm) 48 hr NOEC <0.275 mg/l(mm)	*Thor GmbH: Daphnia magna* 48 hr EC_{50} 1.68 mg/l(mm) 48 hr NOEC 0.882 mg/l(mm)
Chronic toxicity to freshwater invertebrates	*Rohm and Haas: Daphnia magna* 21 d NOEC survival, reproduction, length 0.359 mg/l(mm) 21 d NOEC (dry) weight 0.0442 mg/l(mm)	*Thor GmbH: Daphnia magna* 21 d NOEC survival 0.55 mg/l(mm)
Acute toxicity to saltwater invertebrates	*Rohm and Haas: Americamysis bahia* 96 hr LC_{50} 1.81 mg/l(mm) 96 hr NOEC 1.30 mg/l(mm)	-
Toxicity to freshwater algae	*Rohm and Haas: Pseudokirchneriella subcapitata* 24 hr E_rC_{10} 0.062 mg/l(initial measured) 24 hr E_rC_{50} 0.102 mg/l(initial measured)	*Thor GmbH: Pseudokirchneriella subcapitata* 24 hr E_rC_{10} 0.024 mg/l(initial measured) 24 hr E_rC_{50} 0.114 mg/l(initial measured)
	Geometric mean 24 hr E_rC_{10} = 0.039 mg/l (init.meas.)	
Toxicity to saltwater algae	*Rohm and Haas: Skeletoma costatum* **24 hr E_rC_{10} 0.044 mg/l(initial measured)** 24 hr E_rC_{50} 0.0695 mg/l(initial measured)	-
Toxicity to freshwater sediment dwelling organisms	*Rohm and Haas: Chironomus riparius* 28 d NOEC survival 42.9 mg /kg dry sed. (nom.) 28 d NOEC	-

	developm.rate 13.0 mg/kg dry sed. (nom.) *Lumbriculus variegatus* (oligochaeta) 28 d NOEC, survival 25 mg/kg dry sed. (nom.) *Hyallela azteca* (amphipod) 28 d NOEC, survival 13 mg/kg dry sed. (nom.)	
Inhibition of microbial activity	*Rohm and Haas:* Activated sludge (resp. inhib.) 3 h EC_{50} 41 mg/l	*Thor GmbH:* *Pseudomona putida* (bacteria) 16 h EC_{50} 2.3 mg/l, 16 h NOEC 1.0 mg/L <u>Additional study 1</u> Activated sludge (resp. inhib.) 3 h EC_{50} 13.6 mg/l, **3 h EC_{10} 4.13 mg/L** (municipal STP) <u>Additional study 2</u> Activated sludge (resp. inhib.) 3 h EC_{50} 63.8 mg/l, 3 h EC_{10} 17.0 mg/L (industrial STP) <u>Additional study 2</u> Activated sludge (resp. inhib.) 3 h EC_{50} 45.1 mg/l, 3 h EC_{10} 4.33 mg/L (industrial STP)

Toxicity data of MIT metabolites for aquatic species

Acute toxicity to freshwater fish	*Rohm and Haas:* <u>N-methyl malonamic acid</u> *Oncorhynchus mykiss* 96 hr LC50 >1000 mg/l(nom.) 96 hr NOEC 1000 mg/l(nom.) <u>N-methyl-acetamide</u>	-

	96 hr LC50 >694 mg/l(nom.) 96 hr NOEC 694 mg/l(nom.) Malonamic acid *Oncorhynchus mykiss* 96 hr LC50 >1000 mg/l(nom.) 96 hr NOEC 1000 mg/l(nom.)	
Acute toxicity to freshwater invertebrates	*Rohm and Haas:* N-methyl malonamic acid *Daphnia magna* 48 hr EC_{50} > 1000 mg/l(nom.) 48 hr NOEC 1000 mg/l(nom.) N-methyl-acetamide *Daphnia magna* 48 hr EC_{50} >863 mg/l(mm) 48 hr NOEC 863 mg/l(mm) Malonamic acid *Daphnia magna* 48 hr EC_{50} >1000 mg/l(nom.) 48 hr NOEC 1000 mg/l(nom.)	-
Toxicity to freshwater algae	*Rohm and Haas:* N-methyl malonamic acid *Selenastrum capricornutum* 96 hr NOEC 36 mg/l(mm) 96 hr E_rC_{50} 128 mg/l(mm) N-methyl-acetamide *Selenastrum capricornutum* 72 hr NOEC 0.51 mg/l(nom.) 72 hr E_rC_{50} 5.8 mg/l(nom.) Malonamic acid *Selenastrum capricornutum*	-

	96 hr NOEC 1080 mg/l(mm) 96 hr E_rC_{50} >1080 mg/l(mm)	

Effects on earthworms or other soil non-target organisms

Acute toxicity to Earthworm (*Eisenia foetida*)	*Rohm and Haas:* 14 d LC_{50} = 400 mg/kg dry soil (nom.)	*Thor GmbH:* 14 d LC_{50} = 313 mg/kg dry soil (nom.)
Reproductive toxicity to Earthworm (*Eisenia foetida)*	Not available	

Effects on soil micro-organisms

Nitrogen mineralization	*Rohm and Haas:* EC_{50} = 151 mg/kg dry soil (nom.)	*Thor GmbH:* EC_{50} = 68 mg/kg dry soil (nom.)
Carbon mineralization	*Rohm and Haas:* EC_{50} = 132 mg/kg dry soil (nom.)	*Thor GmbH:* EC_{50} = 317 mg/kg dry soil (nom.)

Effects on terrestrial vertebrates

Acute toxicity to mammals	See chapter 3 of LOE	
Acute toxicity to birds	*Rohm and Haas:* Bobwhite quail (study with CMIT): LD_{50} = 460.71 mg /kg bw (eq. to 64.5 mg a.i./kg bw)	-
Dietary toxicity to birds	*Rohm and Haas:* Bobwhite quail (study with CMIT): LC_0 = 10357 mg /kg (eq. to1450 mg /kg a.i.) LC_{50} = 25257 mg /kg (eq. 3536 mg /kg a.i.) Mallard Duck (study with CMIT): LC_0 = 1614 mg /kg (eq. to 226 mg /kg a.i.) LC_{50} = 6750 mg /kg (eq. to 945 mg /kg a.i.)	-
Reproductive toxicity to birds	Not available	

Effects on honeybees

Acute oral toxicity	Not available
Acute contact toxicity	Not available

Effects on other beneficial arthropods

Acute oral toxicity	Not available
Acute contact toxicity	Not available
Acute toxicity to ……..	Not available

Bioconcentration (Annex IIA, point 7.5)

Bioconcentration factor (BCF)	Not available The log P_{OW} (log octanol: water partition coefficient) for MIT is <1. This value indicates that bioaccumulation of MIT will be minimal. QSAR estimated BCFfish 0.107 l/kg.
Depuration time (DT_{50}) (DT_{90})	Not available
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable

Chapter 6: Other End Points

Effects on Terrestrial plants

Seedling emergence and seedling growth	*Rohm and Haas:* <u>Oilseed rape *(Brassica napus)*</u> NOEC, shoot height and weight 10 mg/kg dry soil (nom.) EC_{50}, shoot weight 36 mg/kg dry soil (nom.) <u>Red clover (*Trifolium pratense*)</u>: NOEC, shoot height and weight 10 mg/kg dry soil (nom.) EC_{50}, shoot weight **18 mg/kg dry soil (nom.)** <u>Rice (*Oryza sativa*)</u> NOEC, shoot height	*Thor GmbH:* <u>Oat (*Avena sativa*)</u>: NOEC, shoot weight 25.0 mg/kg dry soil (nom.) EC_{50}, shoot weight 44.2 mg/kg dry soil (nom.) <u>Oilseed rape (*Brassica napus)*</u> NOEC, shoot weight 12.5 mg/kg dry soil (nom.) EC_{50}, shoot weight 39.9 mg/kg dry soil (nom.) <u>*Pea (Pisum sativum)*</u> NOEC, shoot height

and weight 30 mg a.i./kg dry soil (nom.) EC_{50}, shoot weight 80 mg a.i./kg dry soil (nom.)	and weight 100 mg/kg dry soil (nom.) EC_{50}, emergence, shoot weight and height >200 mg/kg dry soil (nom.)

APPENDIX II: LIST OF INTENDED USES

Experimental data were provided and accepted in support of these intended uses.

Object and/or situation	Product Name	Organisms controlled	Formulation		Application			Applied amount per treatment			Re marks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
PT 12: Slimicides	ACTICIDE® M 20 S	Harmful microorganisms, including bacteria and fungi	SL-Water soluble concentrate	20 % MIT	Automated dosing system	Continuous or shock dosing	Continuous: n.a. Shock: 6 hours	15.0 mg a.s./L	NA	NA	

Appendix III: List of studies

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-A 2	[redacted]	2007	ACTICIDE M 50: 5 Batch Analysis; [redacted] GLP, Unpublished	Y	Thor GmbH
III-A 2	Thor	2007	Sales Specification Acticide M 50; Thor GmbH; Unpublished	Y	Thor GmbH
III-A 2 III-B 2	Thor	2007	Sales Specification Acticide M 20 S; Thor GmbH; Unpublished	Y	Thor GmbH
III-A 2 III-B 2	Thor	2007	Sales Specification Acticide M 10 S; Thor GmbH; Unpublished	Y	Thor GmbH
III-A 3.3	Brauch G	2007	SDB ACTICIDE MIT&A 1021&GB.pdf Thor GmbH; Published	N	Thor GmbH
III-A 3.1.1	[redacted]	1999	Determination of the Melting Point of 2-Methyl-4-isothiazoline-3-one (MIT) according to OECD Guideline No. 102; [redacted]; GLP; Unpublished	Y	Thor GmbH
III-A 3.1.2 III-A 3.10	[redacted]	2002	Determination of the Boilung Point/Boiling Range of 2-Methyl-3(2H)-isothiazolone; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.1.3	[redacted]	2002	Determination of the Density of 2-Methyl-3(2H)-isothiazolone; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.2	[redacted]	2000	2-Methyl-4-isothiazoline-3-one (MIT) - Vapour Pressure; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.2	[redacted]	2006	Determination of the vapour presure of 2-Methyl-2H-isothiazol-3-one (MIT); [redacted]; GLP;	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Unpublished		
III-A 3.4	[redacted]	2006	Spectroscopic Data 2-Methyl-3(2H)-isothiazolone; [redacted] Non- GLP Unpublished	Y	Thor GmbH
III-A 3.4	Matissek R, Lehnguth R	1987	Zur Analytik mikrobiocider Isothiazolone; Fresenius Z Anal Chem 1987/ 328/ pp. 108-111; Non- GLP; Published	No	
III-A 3.4	[redacted]	2007	MIT-Standard and CIT-Standard: UV-Vis absorption spectra; [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 3.4	[redacted]	2007	MIT-Standard and CIT-Standard: IR transmission spectra; [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 3.5-01	[redacted]	1999	Determination of the Water Solubility of 2-Methyl-4-isothiazoline-3-one (MIT) following OECD Guideline No. 105; [redacted]; GLP; Unpublished	Y	Thor GmbH
III-A 3.5-02	[redacted]	2002	Determination of the Water Solubility of 2-Methyl-3(2H)-isothiazolone Including Effect of pH and Temperature; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.6	[redacted]	1996	Dissociation Constant in Water in analogy to OECD-Guideline No. 112 2-Methyl-4-isothiazoline-3-one (MIT) following OECD Guideline No. 105; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.7	[redacted]	1996	Solubility in n-Heptane and Xylene 2-Methyl-4-isothiazoline-3-one (MIT); [redacted]	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			GLP; Unpublished		
III-A 3.7	[redacted]	2007	MIT, Batch No.:LM2000-Solubility in acetonitrile (following A.6 and OECD 105), [redacted]; GLP, Unpublished	Y	Thor GmbH
III-A 3.9-01	[redacted]	2002	Determination of the partitiion Coefficient (n-octanol/water) of the active ingredients of ACTICIDE RS at a range of temperatures and pHs; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.9-02	[redacted]	1993	Determination of the Physico-chemical Properties of ACTICIDE 14 According to EEC Requirements; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.11	[redacted]	2007	MIT, Batch No.:LM2000-Flammability (solids) A.10, Siemens AG, Report No. 20071145.02, November 29, 2007; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.11 III-A 3.15	[redacted]	2003	Thor expert statement for ACTICIDE 14; Thor GmbH; No GLP; Unpublished	Y	Thor GmbH
III-A 3.13 III-B 3.10	[redacted]	2007	Determination of the surface tension of an aqueous solution of MIT (applied as ACTICIDE® M 20) according to OECD 115 resp. EU A.5; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 4.1-01	[redacted]	2007	Determination of 2-Methyl-4-isothiazoline-3-one (MIT) in biocides; [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 4.1-	[redacted]	2007	Determination of 5-Chloro-2-methyl-4-	Y	Thor

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
02			isothiazolin-3-one (CIT) in biocides as an impurity; [redacted] Non- GLP Unpublished		GmbH
III-A 4.1-03	[redacted]	2007	Determination of 4,5-dichloro-2-methyl-4-isothiazolin-3-one (DCMIT) in biocides as an impurity; [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 4.1-04	[redacted]	2007	Determination of chloride in biocides; Thor GmbH; [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 4.2 (b)	[redacted]	2012	HPLC-UV Method for the Determination of MIT in Ambient Air, T[redacted] [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 4.2 (c)	[redacted]	2004	Development and validation of the residue analytical method for 2-Methyl-4-isothiazolin-3-one (MIT) and 5-Chlor-2-methyl-4-isothiazolin-3-one (CIT) in surface water; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 4.3 (d)	[redacted]	2002	Analytical Method for Determination of 2-Methyl-4-isothiazolin-3-one (MIT) and 1,2-Benzisothiazolin-3-one (BIT) in Food Simulants 3 % Acetic Acid, 10 % Ethanol and Olive Oil; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 5	Paulus W	2005	Microbiocide data: Heterocyclic N,S compounds; Directory of Microbicides; pages: 657-671; Non- GLP; Published	No	
III-A 5	Paulus W	2005	Relationship between chemical structure and activity or mode of action of microbicides; Directory of Microbicides;	N	

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			pages: 006-024; Non- GLP; Published		
III-A 5	Williams TM	2006	The Mechanism of Action of Isothiazolone Biocides; Corrosion; NACExpo 2006; Non- GLP; Published	N	
III-A 5.3	[redacted]	2007	MIC values for ACTICIDE M 20; Thor GmbH; [redacted] Non-GLP; Unpublished	Y	Thor GmbH
III-A 5.3	[redacted]	2008	Evaluation of Minimum Inhibitory Concentrations (MIC) for ACTICIDE M 20 against Moulds, Yeasts and Bacteria; [redacted] Non- GLP Unpublished	Y	Thor GmbH
III-A 5.7	[redacted]	2006	Biocide Resistence; Technical Bulletin; [redacted]; Non- GLP; Published	N	Thor GmbH
III-A 5.7	[redacted]	1999	Biocide Resistence; Technical Bulletin; [redacted] Non- GLP; Published	N	Thor GmbH
III-A 6.1.1-01	[redacted]	2000	Acute Oral Toxicity Study of Acticide SR 3267 in Rat; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.1.2-01	[redacted]	2000	Acute Dermal Toxicity Study of Acticide SR 3267 in Rat - Limit Test; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.1.3-011	[redacted]	2000	Acute Inhalation Toxicity Study of Test Item Acticide SR 3267 in Rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.1.4-01/1	[redacted]	2000	Acute Dermal Irritation/Corrosion Test of Acticide SR 3267 in Rabbits; [redacted] Unpublished	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-A 6.1.5-01/1	[redacted]	2000	Sensitization Study of Acticide SR 3267 in Guinea Pig Maximization Test According to Magnusson and Kligman; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.1.5-02	[redacted]	2002	ACTICIDE M 50 - Local Lymph Node Assay (LLNA) in Mice (Identification of contact Allergens); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.2-01	[redacted]	1998	(14C)-CIT and (14C)-MIT: Absorption, distribution, metabolism and excretion following oral administration to the rat; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.2-02	[redacted]	2000	(14C)-CIT and (14C)-MIT: Characterisation of metabolites following oral administration to the rat; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.2-02	[redacted]	1982	^{14}C-Kathon 886 disposition after percutaneous application to male rats; Toxicology department, [redacted] 17.12.1982; Unpublished	N	Rohm and Haas
III-A 6.3.1-01	[redacted]	2002	Repeated Dose 28-Day Oral Toxicity Study of ACTICIDE M 50 in Rats; [redacted] Unpublished	Y	Thor GmbH
III-A 6.3.3 III-A 6.4.3	AgBB Evaluation Scheme	2005	A contribution to the Construction Products Directive: Health-related Evaluation Procedure for Volatile Organic Compounds Emissions (VOC and SVOC) from Building Products; http://www.umweltbundesamt.de/building-products/agbb.htm; AgBB - September 2005, Updated List of LCI values 2005 in Part 3; Non- GLP Published	N	n.a.
III-A	[redacted]	2002	Repeated Dose 90-Day Oral Toxicity	Y	Thor

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
6.4.1-01			Study of ACTICIDE M 50 in Rats; [redacted] GLP; Unpublished		GmbH
III-A 6.4-2	[redacted]	2004	2-Methyl-4-isothiazolin-3-one: A 13-week dietary toxicity study in dogs; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.5-01	[redacted]	2007	MIT: Justification for the submission of a chronic toxicity/oncogenicity study estabished on the combination CIT/MIT (3:1) rather than a chronic/oncogenticity study conducted on MIT; [redacted] Non-GLP Unpublished	Y	Thor GmbH
III-A 6.6.1-1	[redacted]	2000	Investigation of Acticide SR 3267 on Mutagenicity by the Reverse Mutation Assay in Salmonella typhimurium (Ames-test); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.6.2-1	[redacted]	2002	In vitro Mammalian Chromosome Aberration Test of ACTICIDE M 50 with Human Lymphocytes; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.6.3/1	[redacted]	2000	Mutagenic Evaluation of Test Item Acticide SR 3267 in CHO/HPRT Assay; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.6.4-1	[redacted]	2000	Mutagenic Effect of Test Item ACTICIDE SR 3267 by Micronucleus Test; [redacted] [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.6.5/1	[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;	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			[redacted] GLP; Unpublished		
III-A 6.7-02	[redacted]	1994	24-Month Drinking Water Chronic/Oncogenic study in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.8.1-01	[redacted]	2003	A oral (gavage) developmental toxicity study of 2-Methyl-4-isothiazolin-3-one in rabbits; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A6.8.1.b_01	[redacted]	2003	Stump 01RC-269Bsecured_historical control_Doc III A6.8.1.b_01 rabbit teratogenicity.pdf; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.8.1-02	[redacted]	2000	Teratogenicity study of test item ACTICIDE SR 3267 in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.8.2	[redacted]	2003	A Two-Generation reproductive development toxicity study of 2-Methyl-4-isothiazolin-3-one administered via drinking water in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A6.8.2-01	[redacted]	2003	Stump 01RC-285Bsecured_historical control_Doc III A6.8.2_01_2-generation rat.pdf; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.12-01	[redacted]	2007	Medical data for 2-Methyl-2H-isothiazol-3-one, CAS 2682-20-4; [redacted] Unpublished	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-A 6.15.5	AFC Pannel, EFSA	2007	Scientific Opinion of the Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request related to a 16th list of substances for food contact materials; The EFSA Journal (2007) 555-563, 1-31; Report Nº: 66755; Non-GLP; Published	N	
III-A 7.1.1.1.1-02	[redacted]	2002	ACTICIDE 14 - Hydrolysis as a Function of pH; Dr. U. Noack-Laboratorium für Angewandte Biologie; Report Nº: CPH80192; GLP; Unpublished	Y	Thor GmbH
III-A 7.1.1.1.1-03	[redacted]	2002	ACTICIDE 14 - Hydrolysis as a Function of pH (1.2); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.1.1.1.2	[redacted]	1998	(14C)-ACTICIDE 14: Photodegradation in Sterile, Aqueous Solution; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.1.1.2	[redacted]	2007	Activated sludge die away biodegradation test with 2-methyl-2H-isothiazol-3-one (MIT, CAS# 2682-20-4); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.1.1.2.1	[redacted]	2002	ACTICIDE M 50 - Ready Biodegradability Closed Bottle Test; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.1.2.2.1-01	[redacted]	2007	The determination of degradation of 2_Methyl-2H-isothiazol-3-one (MIT, CAS *2682-20-4) in seawater (OECD guideline 309); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A	[redacted]	2007	The determination of the degradation of	Y	Thor

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
7.1.2.2.1-02	[redacted]		2-Methyl-2H-isothiazol-3-one (MIT, CAS * 2682-20-4) in freshwater (OECD guideline 309); [redacted] GLP Unpublished		GmbH
III-A 7.1.3-02	[redacted]	2002	ACTICIDE 14 - Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.2.1	[redacted]	2007	Study for the determination of the degradation of 2-Methyl-2H-isothiazol-3-one (MIT, CAS # 2682-20-4) in soil (OECD 307); [redacted] GLP Unpublished	Y	Thor GmbH
III-A 7.4.1.1-01	[redacted]	1999	ACTICIDE SR 3267: Fish (Bluegill sunfish), Acute Toxicity Test, 96 h, semi-static; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.1.1-02	[redacted]	1999	ACTICIDE SR 3267: Fish (Rainbow trout), Acute Toxicity Test, 96 h, semi-static; [redacted] Unpublished	Y	Thor GmbH
III-A 7.4.1.2-01	[redacted]	1999	ACTICIDE SR 3267: Aquatic Invertebrate Acute Toxicity Test (48 h), Freshwater Daphnids: Daphnia magna STRAUS; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.1.2-03	[redacted]	1998	ACTICIDE SR 3267: Toxicity to Bacteria Pseudomonas putida, Cell Multiplication Inhibition Test; [redacted]	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			[redacted] GLP; Unpublished		
III-A 7.4.1.3-01	[redacted]	1999	ACTICIDE SR 3267: Algal Toxicity, Pseudokirchneriella subcapitata, 96 h; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.1.3-02	[redacted]	2007	Determination of the effect of 2-Methyl-2H-isothiazol-3-one (MIT, CAS# 2682-20-4) on the growth of the marine diatom Skeletoma costatum (International Standard ISO 10253); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.3.2	[redacted]	2006	2-Methyl-2H-isothiazol-3-one (MIT, Applied as Aqueous Formulation ACTICIDE® M 20): An Early Life-Stage Toxicity Test with the Fathead Minnow (Pimephales promelas); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.3.4	[redacted]	2006	2-Methyl-2H-isothiazol-3-one (MIT; Applied as Aqueous Formulation ACTICIDE® M 20): A Flow-Through Life-Cycle Toxicity Test with the Cladoceran (Daphnia magna); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.5.1.1-01	[redacted]	2006	An assessment of the effects of 2-Methyl-2H-isothiazol-3-one (MIT, applied as aqueous formulation ACTICIDE® M 20) on the nitrogen transformation and carbon mineralization activity of soil micro-organisms (OECD 216 and 217 guidelines); [redacted] GLP; Unpublished	No	Thor GmbH
III-A 7.5.1.2-01	[redacted]	2005	An acute toxicity test to determine the effects of 2-Methyl-2H-isothiazol-3-one	No	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
	[redacted]		(MIT, applied as aqueous formulation ACTICIDE M20) on earthworm (Eisenia fetida); [redacted] GLP; Unpublished		
III-A 7.5.1.3	[redacted]	2007	2-Methyl-2H-isothiazol-3-one (MIT, Applied as Aqueous Formulation ACTICIDE® M 20): A Toxicity Test to Determine the Effects on Seedling, Emergence and Growth of Terrestrial Plants; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 2	[redacted]	2000	ACTICIDE M 20S: 5 Batch Analysis; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.1	Brauch G	2007	SDB_ACTICIDE_M_20_S&A_1002&GB_.pdf; Thor GmbH; Non-GLP; Published	Y	Thor GmbH
III-B 3.5	[redacted]	2000	pH value of Acticide M 20S; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.6	[redacted]	2000	Density of Acticide M 20S; [redacted] Unpublished	Y	Thor GmbH
III-B 3.7	[redacted]	2001	The Storage Stability of Acticide M 20S at 20°C; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.7	[redacted]	2000	Stability of ACTICIDE M 20S to Elevated Temperature; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.11	[redacted]	2000	Viscosity of Acticide M 20S; [redacted]	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			GLP;Unpublished		
III-B 5	[redacted]	2007	Acticide M 10S: evaluation of Microbiological Efficacy for Producte Type 13; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 5	[redacted]	2004	Acticide M 20 Examination of microbiological efficacy for Product Type 6 (Definition in Annex V of 98/8/EC); [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 5.10(3)	[redacted]	2007	Acticide M 10S: evaluation of Microbiological Efficacy for Producte Type 6; [redacted]; Non-GLP; Unpublished	Y	Thor GmbH
III-B 5.10(4)	[redacted]	2008	ACTICIDE M 10 S: Examination of microbiological efficacy for Product Type 13; [redacted] Non-GLP; Unpublished	Y	Thor GmbH
III-B 6.1.1.-01	[redacted]	2005	Acute Oral Toxicity study (fixed dose method) of test item ACTICIDE M 10S in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 6.1.2.-01	[redacted]	2005	Acute dermal toxicity study of test item ACTICIDE M 10S in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 6.1.3.-01	[redacted]	2006	Acute Inhalation Toxicity Study of Test Item ACTICIDE M10S in Rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 6.2.-01	[redacted]	2005	Acute skin irritation study of test item Acticide M10 S in rabbits;	Y	Thor GmbH

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			[redacted] GLP; Unpublished		
III-B 6.2.-02	[redacted]	2005	Acute eye irritation study of test item Acticide M 10 S in rabbits; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 6.3.-01	[redacted]	2001	Methylisothiazolinone 20% - Open Epicutaneous Test in Guinea Pigs; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 6.3.-02	[redacted]	2005	Skin sensitization of test item Acticide M 10 S in Guinea Pigs by Magnusson and Kligman; [redacted] GLP; Unpublished	Y	Thor GmbH