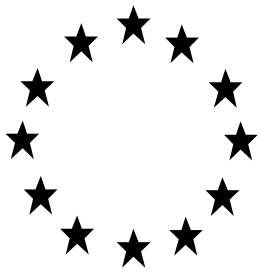
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



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

Product type 11

(Preservative for Liquid Cooling and Processing Systems)

January 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 (MIT) in product-type 11 (Preservatives for liquid-cooling and processing systems), carried out in the context 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 11.

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(2H)-one for product-type 11 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.

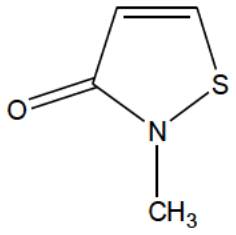
For the implementation of the common principles of Annex VI, the content and conclusions of the assessment report, which is available from the web-site of ECHA, shall be taken into account.

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/m^3 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 Effectiveness

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 for preservation of open and closed liquid cooling and processing systems against harmful microorganisms in end concentration of 0.0005 % 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 % is 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, C(M)IT: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 C(M)IT/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 C(M)IT/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 C(M)IT/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 methylisothiazolinone (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 C(M)IT/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, increased respiration rate) laboured breathing	LC_{50} = 0.11-0.19 mg/l	A6.1.3a/01, A6.1.3a/02, A6.1.3-1
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
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 cooling and processing liquids 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**
$AEL_{short\text{-}term}$	Rabbit developmental study, 90-days rat study	10 mg/kg bw/day	100, 0.53 correction factor for oral abs.	0.053 mg/kg bw/day
$AEL_{medium\text{-}term}$	Rabbit developmental study, 90-days rat study	10 mg/kg bw/day	100, 0.53 correction factor for oral abs.	0.053 mg/kg bw/day
$AEL_{long\text{-}term}$	Rabbit developmental study, 90-days rat study	10 mg/kg bw/day	200, 0.53 correction factor for oral	0.027 mg/kg bw/day

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

*- the exposure was compared to short- and medium-term NOAEC and AEC for C(M)IT/MIT (3:1).
**- the exposure was compared to long-term NOAEC and AEC for C(M)IT/MIT (3:1).

2.2.1.2 Exposure assessment and risk characterisation

Summary table: scenarios in preservation of liquid cooling and processing systems			
Scenario number	**Scenario**	**Primary or secondary exposure Brief description of scenario**	**Exposed group**
1.	Manual loading into the sump	Primary exposure ACTICIDE® M 20S can be administrated manually, depending on the size of the system. The TNsG describes that these systems are normally dosed from biocide reservoirs, with the supply and maintenance of the dosing systems under the control of the biocide suppliers (water treatment professionals). Biocide addition to medium sized systems is by intermittent (1 per week) or continuous dosing. For very small and very large systems, the biocides are added by shock dosing. Biocides may be administered by dosimeter or by manual addition of a measured quantity (e.g. graduated jug) or for large systems pouring several entire drums in an area of the system to allow adequate mixing. The number of systems per site may range from 1 to 20 or more depending on the size of the facility. A default of 3 systems per site is proposed in TNsG, Part 2 June 2002; PT11.02). It is also stated in the TNsG that manual addition of biocidal concentrates occurs at each facility (3 systems/installation) once a week for 2 minutes.	Professionals
2.	Automated loading into the sump	Primary exposure The biocidal product is supplied in IBCs of 25 – 1000 kg. The IBC has to be connected to an automated dosing system about once per week (to once per month) depending on the individual cooling system. The connection procedure takes about 20 minutes as it is stated by the applicant. The exposure during automated transfer would be very low and exceptionally can occur through changing the drum of concentrate and moving/connecting the dispensing tube. Frequency and duration for changing out the drum and transferring the dip tube suggested in the TNsG (2002) indicates a service company will visit 4 facilities per day with 3 units per facility (corresponds to 12 systems/day) at 2 minutes per unit (24 minutes total potential exposure time per day). Since data provided by the applicant derived from the questionnaire on MIT usage patterns seems to be more realistic than defaults from the TNsG, these data will be used for the exposure estimation.	Professionals

3.	Sampling process liquid (dip slide)	Primary exposure Routine testing of the cooling water is conducted via a dip slide to monitor for microbial contamination. The TNsG (2002) describes that plant workers inspect and test the system to monitor for scale or biofilm accumulation at each facility (3 systems/facility) on a weekly basis. This task takes 2 minutes per system or 6 minutes to inspect and test 3 systems (TNsG, 2002). Applicant provided the scenario that specially trained operators take weekly (up to half yearly) water samples for routine analysis of water parameter (chemical/microbiological). Sample drawing may take 10 minutes.	Professionals
4.	Cleaning dispensing pumps and empty drums	Primary exposure It is stated by the applicant that the IBCs have to be cleaned regularly taking 15 minutes (weekly – monthly) because drums are returned to the supplier for re-use. The wastewater is discharged automatically. Maintenance of dosing pumps requires the cleaning of these items before dismantling (TNsG, 2002). This task is considered to be intermittent, therefore it is assumed to be covered by the time for cleaning empty drums.	Professionals
5.	Inhalation of spray drift from preserved cooling water	Primary exposure Professionals may work in the vicinity of the cooling towers and could be exposed through inhalation of spray from preserved cooling water. It is stated in the TNsG (Part 2, June 2002) that effective drift eliminators prevent exposure to cooling tower aerosols and volatilised biocides are released to the environment. Very large systems do not use drift eliminators, but the release source is many tens of meters above ground level.	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 - Manual loading into the sump	Tier 1/ no PPE	$3.92 \cdot 10^{-4}$	2.02	2.02
	Tier 2/ PPE	$3.92 \cdot 10^{-4}$	$2.02 \cdot 10^{-2}$	$2.02 \cdot 10^{-2}$
Scenario 2 - Automated loading into the sump	Tier 1/ no PPE	-	$6.13 \cdot 10^{-2}$	$6.13 \cdot 10^{-2}$
	Tier 2/ PPE	-	$6.13 \cdot 10^{-3}$	$6.13 \cdot 10^{-3}$
Scenario 3 - Sampling process liquid (dip slide)	Tier 1/ no PPE	$5.73 \cdot 10^{-9}$	$3.44 \cdot 10^{-5}$	$3.44 \cdot 10^{-5}$
Scenario 4 - Cleaning dispensing pumps and empty drums	Tier 1/ no PPE	$3.44 \cdot 10^{-6}$	$2.75 \cdot 10^{-2}$	$2.75 \cdot 10^{-2}$
	Tier 2/ PPE	$3.44 \cdot 10^{-6}$	$2.27 \cdot 10^{-3}$	$2.27 \cdot 10^{-3}$
Scenario 5 - Inhalation of spray from preserved cooling water	Tier 1/ no PPE	$7.29 \cdot 10^{-6}$	-	$7.29 \cdot 10^{-6}$

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)
Manual loading into the sump, Tier 1, no PPE	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	2.02	7481	No
Manual loading into the sump, Tier 2, PPE*	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$2.02 \cdot 10^{-2}$	75	Yes
Automated loading into the sump, Tier 1, no PPE	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$6.13 \cdot 10^{-2}$	227	No
Automated loading into the sump, Tier 2, PPE*	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$6.13 \cdot 10^{-3}$	23	Yes
Sampling process liquid (dip slide)	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$3.44 \cdot 10^{-5}$	0	Yes
Cleaning dispensing pumps and empty drums, Tier 1, no PPE	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$2.75 \cdot 10^{-2}$	102	No
Cleaning dispensing pumps and empty drums, Tier 2, PPE*	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$2.27 \cdot 10^{-3}$	8	Yes
Inhalation of spray drift from preserved cooling water	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$7.29 \cdot 10^{-6}$	0	Yes
Scenarios 1+3+4+5: Manual loading (Tier 2) + sampling process liquid (Tier 1) + cleaning dispensing pump and empty drums (Tier 2) + inhalation of spray drift from preserved cooling water (Tier 1)	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$2.29 \cdot 10^{-2}$	85	Yes
Combined exposure (Automated loading (Tier 2) + sampling process liquid (Tier 1) + cleaning dispensing pump and empty drums (Tier 2)+ inhalation of vapours (Tier 1)	$AEL_{long\text{-}term}$ 0.027 mg/kg bw/day	$8.44 \cdot 10^{-3}$	31	Yes

*PPE considered: protective gloves, impermeable coverall, face mask

Scenario, Tier, RPE	Relevant reference value	External inhalation exposure mg/m³ (8 hrs-TWA)	Estimated exposure/ long-term AEC_{inh} (%)	Acceptable (yes/no)
Manual loading into the sump, Tier 1, 2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/m³	$2.35 \cdot 10^{-3}$	11.19	Yes
Automated loading into the sump, Tier 1,2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/m³	Negligible	n/a	Yes
Sampling process liquid (dip slide), Tier 1, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/m³	$3.44 \cdot 10^{-8}$	$1.64 \cdot 10^{-6}$	Yes
Cleaning dispensing pumps and empty drums, Tier 1,2, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/m³	$2.06 \cdot 10^{-5}$	$9.81 \cdot 10^{-4}$	Yes
Inhalation of spray drift from preserved cooling water, Tier 1, no RPE	Long-term $AEL_{inhalation}$ 0.021 mg/m³	$4.38 \cdot 10^{-5}$	$2.09 \cdot 10^{-3}$	Yes

Conclusion of risk characterisation for professional user

Scenario, Tier	SCL for dermal effects	Deposit on hands	Acceptable (yes/no)
Manual loading into the sump, Tier 1, no PPE	0.0015 %	20 %	No
Manual loading into the sump, Tier 2, PPE*	0.0015 %	20 %	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)	0.0015 %	0.0005 %	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
Inhalation of spray drift from preserved cooling water	0.0015 %	0.05	Yes

* - the technical and organizational RMM adequate for high hazard chemicals and appropriate PPE
**- appropriate protective gloves and impermeable coverall

According to the exposure calculation estimates of systemic exposure to MIT during manual loading of ACTICIDE® M 20S into the sump is acceptable, if professional is wearing protective gloves, impermeable coverall and facemask. However, the manual loading is not acceptable due to very high hazard for local skin effects during this task if performed manually and therefore manual loading was not further considered in combined systemic risk assessment.

The estimated systemic exposure of professional to MIT is below the reference value during automated loading of ACTICIDE® M 20S 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 or cooling liquids by dip sliding the professional's exposure is estimated to be below the $AEL_{long\text{-}term}$ and therefore acceptable. The concentration of MIT in cooling/processing liquid is below the concentration limit for skin sensitization. Thereafter the risk of local dermal effects is acceptable.

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

Professionals working in the vicinity of preserved cooling or processing liquids might be exposed to MIT spray drift by inhalation. However, their exposure to MIT is calculated to be below the reference value for systemic and local respiratory effects.
Assuming one person performing different tasks on the same day, the combined exposure was estimated assuming a person automatically loading ACTICIDE® M 20S into the sump, monitoring the liquid by slide dipping, cleaning dispensing pumps and empty drums and inhaling the spray drift of MIT during that day. The combined exposure for systemic effects is considered to be acceptable when ACTICIDE® M 20S will be used for preservation of cooling and processing liquids according to the instructions for use.

Conclusion of risk characterisation for non-professional user

The biocidal product ACTICIDE® M 20S is intended under PT 11 only for professional use.

Conclusion of risk characterisation for indirect exposure

General public could potentially be exposed to MIT in aerosols from cooling towers. The risk for general public, being exposed in such way is considered to be covered by the risk assessment made for professional workers inhaling spray drift from preserved cooling water. Thereafter it can be concluded that the risk for local respiratory effects for general public is acceptable.

2.2.2 Environmental Risk Assessment

2.2.2.1 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. 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 °C was -0.32. The BCF_{fish} 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	Experimental value at standard conditions (20 °C and pH 7)
Organic carbon/water partition coefficient (Koc)	7.5	l/kg	Arithmetic mean (AR MIT, 2014)
Henry's Law Constant (20 °C)	$<4.39 \cdot 10^{-5}$	Pa m^3/mol	
Biodegradability	Not ready biodegradable		
DT_{50} for STP	0.04	day	Value from experimental flow-through study.
DT_{50} for biodegradation in water/sediment	2.21	day (at 12 °C)	Geometric mean value for whole system from experiments with freshwater water/sediment systems
DT_{50} for hydrolysis in surface water	$1 \cdot 10^6$	day (at 12 °C /pH 7)	Default value in EUSES (surrogate zero)
DT_{50} for photolysis in surface water	18.1	day	Highest value from experimental studies (n=2)
DT_{50} for degradation in soil	0.51	day (at 12°C)	Highest value from experimental studies
DT_{50} for degradation in air	16.6	hr	Atkinson calculation method

2.2.2.2 Hazard identification and effects assessment

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.

A cell multiplication test with *P. putida* was conducted in accordance with EN ISO 10712, resulting in a 16-hour EC_{50} of 2.3 mg a.i./l. An assessment factor of 10 was used to derive the $PNEC_{STP}$ from the EC_{50}.

$PNEC_{STP}$ = 0.23 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/l or 3.39 µg a.i./l

Summary table on calculated PNEC values	
STP	0.23 mg/l*
Soil	0.0417 mg/kg (wet wt)

* Additional endpoints regarding the effect of MIT on microorganisms in STP support a refined PNEC which is to be considered at the product authorization stage.

2.2.2.3 Exposure assessment and risk characterisation

Summary table on compartments exposed and assessed		
Compartment	**Exposed (Y/N)**	**Assessed (Y/N)**
STP	Y	Y
Surface water	Y	Y
Sediment	Y	Y
Soil	Y	Y
Groundwater	Y	Y
Air	Y	Y

MIT is used in open or closed re-circulating systems at continuous dosing (open recirculating systems only) and shock dosing (open and closed recirculating systems). The focus of the exposure assessment and risk characterisation was on open recirculating cooling systems. The cooling water circulates in an open loop. Water that has passed through the heat exchangers is returned to a cooling tower where the temperature is lowered by evaporative cooling. The cooled water is re-collected and re-circulated into the system. A certain amount of the cooling water is purged from the system (= blow down) to prevent scaling which is compensated by so called fresh "make-up" water. Open recirculating cooling systems are considered to represent the highest exposure potential to water and to wastewater and therefore to cover the closed systems.

Different scenarios were assessed for small and large open recirculating cooling systems. The relevant routes of surface water exposure for small open recirculating systems are either through the direct discharge of cooling water from the systems into receiving waters, or through the discharge from sewage treatment plants (STP) treating wastewater from the cooling water systems. For small open recirculating systems scenarios with continuous dosing, shock dosing twice daily and shock dosing twice weekly were considered.

For the large open recirculating systems, discharge to an STP is not considered realistic in view of the large volume of water treated. Therefore, only a direct release to surface water, and to air and soil through the drift have been assumed. For large open recirculating systems scenarios with continuous dosing and shock dosing twice daily were considered.

Exposure assessment

In **Tier 1**, the surface water exposure assessment has been carried out based on the fraction directed to water derived from the STP simulation study. In **Tier 2**, the surface water exposure assessment has been carried out based on the fraction directed to water given by Simple Treat model.

Analogous to the soil exposure assessment in the C(M)IT/MIT CAR a fraction of 0.0664 MIT in sludge has been considered as a relevant worst case value to use in the **Tier 1** soil exposure assessment. The fraction of 0.0664 in the sludge represented the total radioactivity measured in this compartment derived from the STP simulation study and not the parent compound only. Considering the low potential of adsorption of MIT (Koc = 7.5 $l.kg^{-1}$) the fraction adsorbed onto sludge given by Simple Treat model (Fstp sludge = 0.0007) seems to be more realistic for the active ingredient MIT. Hence, a fraction of 0.0007 in sludge has been considered as a more realistic value to use in the **Tier 2** soil exposure assessment.

Summary table on calculated PEC values – Small open recirculating systems					
Scenario	**PEC_{STP}**	**PEC_{water}**	**PEC_{soil}**	**PEC_{GW}**	**PEC_{air}**
	[mg/l]	[mg/l]	[mg/kg_{wwt}]	[µg/l]	[mg/m^3]
Direct release to surface water Continuous dosing	-	0.50 (dilution 10) $2.5 \cdot 10^{-2}$ (dilution 200) $5.0 \cdot 10^{-3}$ (dilution 1000)	0.130 (no drift reduction) $1.30 \cdot 10^{-3}$ (drift eliminator)	9.158 – 12.179[1] (Jokioinen, no drift reduction) < 0.001 – 0.002[1] (others, no drift reduction) 0.006 – 0.008[1] (Jokioinen, drift eliminator)	-
Direct release to surface water Shock dosing, T_{int} = 12 hr	-	4.41 (dilution 10) 0.221 (dilution 200) $4.4 \cdot 10^{-2}$ (dilution 1000)	1.07 (no drift reduction) $1.07 \cdot 10^{-2}$ (drift eliminator)	162.0 – 213.8[1] (Jokioinen, no drift reduction) < 0.001 – 0.026[1] (others, no drift reduction) 0.217 – 0.291[1] (Jokioinen, drift eliminator)	-
Direct release to surface water Shock dosing, T_{int} = 84 hr	-	0.59 (dilution 10) $3.0 \cdot 10^{-2}$ (dilution 200) $5.9 \cdot 10^{-3}$ (dilution 1000)	0.154 (no drift reduction) $1.54 \cdot 10^{-3}$ (drift eliminator)	11.57 – 15.40[1] (Jokioinen, no drift reduction) 0.008 – 0.011[1] (Jokioinen, drift eliminator)	-
Release to STP Continuous dosing	$1.46 \cdot 10^{-2}$ (Tier 1) $2.00 \cdot 10^{-2}$ (Tier 2)	$1.46 \cdot 10^{-3}$ (Tier 1) $2.00 \cdot 10^{-3}$ (Tier 2)	$1.65 \cdot 10^{-2}$ (Tier 1) $1.74 \cdot 10^{-4}$ (Tier 2)	0.270 (Tier 1)[2] $2.84 \cdot 10^{-3}$ (Tier 2)[2]	$3.34 \cdot 10^{-5}$
Release to STP Shock dosing, T_{int} = 12 hr	0.120 (Tier 1) 0.165 (Tier 2)	$1.2 \cdot 10^{-2}$ (Tier 1) $1.65 \cdot 10^{-2}$ (Tier 2)	0.271 (Tier 1) $2.86 \cdot 10^{-3}$ (Tier 2)	4.43 (Tier 1)[2] $4.67 \cdot 10^{-2}$ (Tier 2)[2]	$2.74 \cdot 10^{-4}$
Release to STP Shock dosing, T_{int} = 84 hr	$1.73 \cdot 10^{-2}$ (Tier 1) $2.37 \cdot 10^{-2}$ (Tier 2)	$1.73 \cdot 10^{-3}$ (Tier 1) $2.37 \cdot 10^{-3}$ (Tier 2)	$3.89 \cdot 10^{-2}$ (Tier 1) $4.10 \cdot 10^{-4}$ (Tier 2)	0.636 (Tier 1)[2] $6.71 \cdot 10^{-3}$ (Tier 2)[2]	$3.94 \cdot 10^{-5}$
[1] Calculated with PEARL 4.4.4 modelling [2] Estimated based on predicted concentration in pore water					

Note: A higher PEC_{soil} was calculated for soil exposure following direct emission to air due to the evaporation and wind drift compared to exposure via sludge amendment in Tier 2. Regarding soil exposure following direct emission to air due to the evaporation and wind drift there is no difference between small open recirculating cooling systems whether there is connection to the STP or not. Consequently, higher tier calculations with PEARL 4.4.4 modelling are also applicable to use of MIT in small open recirculating systems with release to STP.

Summary table on calculated PEC values - Large open recirculating systems					
Scenario	**PEC_{water}**	**PEC_{soil}**	**PEC_{soil}**	**PEC_{GW}[4]**	**PEC_{air}**
	[mg/l]	[mg/kg_{wwt}]	[mg/kg_{wwt}]	[µg/l]	[mg/m^3]
Continuous dosing	0.50 (Tier 1)[1] $2.5 \cdot 10^{-2}$ (Tier 2A)[2] $5.0 \cdot 10^{-3}$ (Tier 2B)[3]	23.4 (no drift reduction) 0.234 (drift eliminator)	46.9 (no drift reduction) 0.469 (drift eliminator)	0.329 – 0.682 (Hamburg, no drift reduction) 8089 – 10574 (Jokioinen, no drift reduction) 0.949 - 0.974 (Piacenza, no drift reduction) < 0.001 – 0.084 (others, no drift reduction) 20.85 – 27.63 (Jokioinen, drift eliminator) < 0.001 – 0.004 (others, drift eliminator)	$6.00 \cdot 10^{-3}$
Shock dosing, T_{int} = 12 hr	0.58 (Tier 1)[1] $2.9 \cdot 10^{-2}$ (Tier 2A)[2] $5.8 \cdot 10^{-3}$ (Tier 2B)[3]	27.2 (no drift reduction) 0.272 (drift eliminator)	54.5 (no drift reduction) 0.545 (drift eliminator)	0.401 – 0.833 (Hamburg, no drift reduction) 9735– 12719 (Jokioinen, no drift reduction) 0.059 – 0.102 (Kremsmuenster, no drift reduction 0.938 – 1.160 (Piacenza, no drift reduction) < 0.001 – 0.059 (others, no drift reduction) 0.929 – 1.238 (Jokioinen, drift eliminator) < 0.001 (others, drift eliminator)	$6.97 \cdot 10^{-3}$

[1] Dilution 10 *Large cooling system + limited river* (worst case)

[2] Dilution 200 *Large cooling system + moderate river*

[3] Dilution 1000 *Large cooling system + large/medium river*

[4] Calculated with PEARL 4.4.4 modelling

Risk characterization

Summary table on calculated PEC/PNEC values			
Scenario	**PEC/PNEC$_{STP}$**	**PEC/PNEC$_{water}$**	**PEC/PNEC$_{soil}$**
Small open recirculating systems - Direct release to surface water Continuous dosing	-	**129** (dilution 10) **6.4** (dilution 200) **1.29** (dilution 1000)	**3.1** (no drift reduction) 0.031 (drift eliminator)
Small open recirculating systems – Direct release to surface water Shock dosing, T_{int} = 12 hr	-	**1131** (dilution 10) **57** (dilution 200) **11.3** (dilution 1000)	**26** (no drift reduction) 0.26 (drift eliminator)
Small open recirculating systems – Direct release to surface water Shock dosing, T_{int} = 84 hr	-	**152** (dilution 10) **7.6** (dilution 200) **1.52** (dilution 1000)	**3.7** (no drift reduction) 0.037 (drift eliminator)
Small open recirculating systems – Release to STP Continuous dosing	0.063 (Tier 1) 0.068 (Tier 2)	0.37 (Tier 1) 0.40 (Tier 2)	0.40 (Tier 1) 0.004 (Tier 2)
Small open recirculating systems – Release to STP Shock dosing, T_{int} = 12 hr	0.52 (Tier 1) 0.72 (Tier 2)	**3.1** (Tier 1) **4.2** (Tier 2)	**6.5** (Tier 1) 0.07 (Tier 2)
Small open recirculating systems – Release to STP Shock dosing, T_{int} = 84 hr	0.075 (Tier 1) 0.10 (Tier 2)	0.44 (Tier 1) 0.61 (Tier 2)	0.93 (Tier 1) 0.01 (Tier 2)
Large open recirculating systems – Direct release to surface water Continuous dosing	-	**129** (dilution 10) **6.4** (dilution 200) **1.29** (dilution 1000)	**1125** (no drift reduction) **11.25** (drift eliminator)
Large open recirculating systems – Direct release to surface water Shock dosing, T_{int} = 12 hr	-	**149** (dilution 10) **7.4** (dilution 200) **1.49** (dilution 1000)	**1304** (no drift reduction) **13.04** (drift eliminator)

Note: A higher PEC$_{soil}$ was calculated for soil exposure following direct emission to air due to the evaporation and wind drift compared to exposure via sludge amendment in Tier 2. Regarding soil exposure following direct emission to air due to the evaporation and wind drift there is no difference between small open recirculating cooling systems whether there is connection to the STP or not. Consequently, drift eliminators are also required for an acceptable risk to soil organisms following the use of MIT in small open recirculating systems with indirect releases via STP.

Conclusion

Atmosphere

Risks relevant to biotic and abiotic effects to the atmosphere are negligible due to the low concentrations of MIT in the air and expected rapid degradation.

Sewage treatment plants

$PEC/PNEC_{STP}$ values calculated from the proposed use of ACTICIDE® M 20S as preservative in open recirculating cooling systems are below 1, indicating acceptable risks to organisms involved in the biological processes of the sewage treatment works.

Aquatic compartment

The assessment indicates for the continuous dosing regime unacceptable risks to the organisms in the water column (freshwater) following direct release to surface water and acceptable risk to the organisms in the water column (freshwater) following indirect release via STP. For shock dosing twice per day the assessment indicates unacceptable risk to the organisms in the water column (freshwater) following direct release from small and large systems to surface water and unacceptable risk to the organisms in the water column (freshwater) following indirect release from small systems via STP. For shock dosing twice per week the assessment indicates unacceptable risk to the organisms in the water column (freshwater) following direct release from small and large systems to surface water and acceptable risk to the organisms in the water column (freshwater) following indirect release from small systems via STP.

Terrestrial compartment

The PEC/PNEC values calculated for the large and small open recirculating systems indicate unacceptable risk resulting from the drift deposition. As shown in the table the PEC/PNEC values calculated for the large open recirculating systems using drift eliminators still indicate unacceptable risk to soil organisms resulting from the drift deposition for both continuous and shock dosing. PEC/PNEC values calculated for the small open recirculating systems using drift eliminators indicate acceptable risk to soil organisms resulting from the drift deposition following both continuous and shock dosing.

Groundwater

Predicted concentration in groundwater resulting from drift deposition by the large open recirculating systems with direct release to surface water are above the limit 0.1 µg/L set up for pesticides in the scenarios Hamburg, Jokioinen and Piacenza and below the limit in the other FOCUS scenarios following continuous dosing. Predicted concentration in groundwater resulting from drift deposition by the large open recirculating systems with direct release to surface water are above the limit 0.1 µg/L set up for pesticides in the scenarios Hamburg, Jokioinen, Kremsmuenster and Piacenza and below the limit in the other FOCUS scenarios following shock dosing twice per day. Both for continuous and shock dosing regimes predicted concentration in groundwater resulting from drift deposition by the small open recirculating systems with direct release to surface water are above the limit 0.1 µg/L set up for pesticides in the scenario Jokioinen and below the limit in the other FOCUS scenarios.
Both for continuous and shock dosing regimes predicted concentration in groundwater resulting from drift deposition by the large open recirculating systems using drift eliminators are below the limit 0.1 µg/L set up for pesticides in all FOCUS scenarios except

Jokioinen. Predicted concentration in groundwater resulting from drift deposition by the small open recirculating systems using drift eliminators are below the limit 0.1 µg/L set up for pesticides in all FOCUS scenarios in case of continuous dosing and shock dosing twice per week. For shock dosing twice per day predicted concentration in groundwater resulting from drift deposition by the small open recirculating systems using drift eliminators are below the limit 0.1 µg/L set up for pesticides in all FOCUS scenarios except Jokioinen.
The concentrations in pore water (surrogate for groundwater) are far below 0.1 µg/L set up for pesticides for the small cooling systems with indirect emission via STP in Tier 2 approach. Tier 2 estimates based on pore water concentrations are in most situations very conservative, as they do not take into account the very rapid degradation of MIT in soil.

2.2.3 PBT and POP assessment

MIT does not fulfill the PBT/vPvB criteria and can therefore not be considered a PBT/vPvB substance. It does not fulfill 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 fulfill the P/vP-criterion.

2.2.4 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 11 is specified in the BPC opinion following discussions at the 18. 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

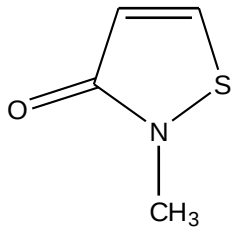
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

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 11: Preservative for Liquid Cooling and Processing Systems

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 used
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:* Solubility in hexane: 2.42 g/l at 30 ºC 0.93 g/l at 10 ºC Solubility in ethyl acetate: > 1000 g/l at 30 ºC 562.15 g/l at 10 ºC	*Thor GmbH:* 1.46 g/l in n-hexane at 21 °C 143.6 g/l in xylene 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 Category	Hazard Statement
Acute Tox. 3 (oral) Acute Tox. 3 (dermal) Acute Tox. 2 (inhalation) Skin Corr. 1B STOT Single 3 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. H335; May cause respiratory irritation.

with regard to fate and behaviour data

-

with regard to ecotoxicological data

Hazard Class and Catagory	Hazard Statement
Aquatic Acute 1 (M=10) Aquatic Chronic 1 (M=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.

*As proposed in RAC opinion on harmonized classification and labeling of MIT adopted 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	*Thor GmbH:* Not submitted; an active substance will not

	by reversed phase HPLC with UV detection (275 nm); LOQ = 0.05 µg/g of soil or sediment.	be present in soil due to high mobility and fast 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-	*Thor GmbH:* 67-69 % at 50 mg base-eq./kg b.w. (rat)

	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 a aqueous solution 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 60 min. (human epidermal construct); non-corrosive after 3 min. 1.7 % non-corrosive (3	*Thor GmbH:* Corrosive; 0.5 ml of MIT applied undiluted (rabbit)

	and 60 min). 21-day cumulative skin irritation (humans): not irritant ≤ 500 ppm (39.5 μg/cm²)	
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 SCL for skin sensitization ≥0.0015 %*

* RAC proposal, March 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/cm²] (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 mg/kg bw/day (1500 ppm), based on transient decreased body weight gain and food consumption	*Thor GmbH:* NOAEL = 30 mg a.i./kg bw/day; 3 months (rat, gavage). LOAEL not determined.

Lowest relevant dermal NOAEL / LOAEL	*Rohm and Haas:* Test with C(M)IT/MIT (3:1): 90 days NOAEL (rabbit) was not determined; LOAEL = 0.1 mg C(M)IT/MIT/kg bw/day (100 ppm); irritation at site of contact 30 months NOEL (mouse) = 400 ppm C(M)IT/MIT (3:1). There were no systemic toxic effects in this study.
Lowest relevant inhalation NOAEC / LOAEC	*Rohm and Haas, Thor GmbH:* Test with C(M)IT/MIT (3:1): 90 days NOAEC (rat) = **0.34 mg C(M)IT/MIT (3:1)/m³** based on irritation to the respiratory tract. 90 days LOAEC (rat) = 1.15 mg C(M)IT/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:* <u>N-methyl malonamic acid (NMMA)</u>: 90 days NOEL (diet, rat) = 13-15 mg NMMA/kg bw/day (100-220 ppm), the highest dose tested. <u>Malonamic acid (MA)</u>: 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:* <u>Genotoxicity *in vitro*:</u> 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. <u>Genotoxicity *in vivo*:</u> negative in micronucleus assay in mouse bone marrow and in UDS assay in rat hepatocytes.	*Thor GmbH:* <u>Genotoxicity *in vitro*:</u> 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. <u>Genotoxicity *in vivo*:</u> negative in micronucleus assay in mouse bone 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 C(M)IT/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 C(M)IT/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/day	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 C(M)IT/MIT (3:1) in rat	8
Inhalation AEC (long-term)	0.021 mg/m^3	90-days inhalation study with C(M)IT/MIT (3:1) in rat	16
Dermal NOAEC	0.0015% (15 ppm)	Based on animal and human data	N/A
Drinking water limit	Not required.	N/A	N/A
ARfD (acute reference dose)	0.1 mg/kg bw/day	Rabbit developmental	100

	study	

* 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).

Acceptable exposure scenarios (including method of calculation)

<table>
<tr><td>Professional users</td><td>PT11
The representative biocidal product ACTICIDE® M 20S (20 % MIT) for use in product type 11, in preservation of liquid cooling and processing systems at concentration of MIT 5 ppm was evaluated. Both continuous and shock dosing were considered.

Operator’s exposure assessment for this product type includes exposure from mixing the biocidal product into the cooling system, post-application tasks (sampling process liquid (dip slide), cleaning dispensing pumps and empty containers) and secondary exposure from inhalation of spray drift from preserved cooling water.</td></tr>
<tr><td></td><td>Exposure assessment is based on simple database models listed below:
<table><tr><td></td><td>Relevant model</td></tr><tr><td>Mixing and loading phase – Automated loading:</td><td>RISKOFDERM Toolkit
Connecting lines</td></tr><tr><td>Post application phase:
- sampling process liquid (dip slide)
- cleaning dispensing pumps and empty containers</td><td>BEAT database (2008) ‘Cleaning of spray equipment’</td></tr><tr><td>Secondary exposure: Inhalation of spray drift from preserved cooling water</td><td>TnsG Part 3 June 2002, Appendix 6.1</td></tr></table></td></tr>
<tr><td></td><td>PPE: Appropriate risk mitigation measures must be applied during different phase of use of the ACTICIDE® M 20S (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 (protective gloves) and cleaning pumps and empty drums (impermeable coverall, gloves and face shield)</td></tr>
<tr><td>Non-professional users</td><td>Non-professional use is not envisaged.</td></tr>
<tr><td>Indirect exposure as a result of use</td><td>Inhalation of spray drift from preserved cooling water The risk assessment for general public is covered by risk assessment for professionals indirect exposure.</td></tr>
</table>

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 <u>Ready biodegradation tests with metabolites</u> N-methyl malonamic acid: Yes N-methyl acetamide: Yes Malonamic acid: Yes	*Thor GmbH:* No 0 % biodegradation in Closed Bottle Test
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 applied activity after 30 days of incubation.	*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
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:*	*Thor GmbH:*

Ka_{oc} , Kd_{oc}	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 $Kads_{oc}$ 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 = $2.9 \cdot 10^{-25}$ 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 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.	*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 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 mg/l(mm) growth	*Thor GmbH: Pimephales promelas* 33 d NOEC 2.1 mg/l (mm, survival)
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	*Thor GmbH: Daphnia magna* 21 d NOEC survival 0.55 mg/l(mm)

	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 EC50 41 mg/l	*Thor GmbH: Pseudomona putida* (bacteria) **16 h EC50 2.3 mg/l**

Toxicity data of MIT metabolites for aquatic species

Acute toxicity to freshwater fish	*Rohm and Haas:* N-methyl malonamic acid *Oncorhynchus mykiss* 96 hr LC50 > 1000 mg/l (nom.) 96 hr NOEC 1000 mg/l (nom.) N-methyl-acetamide 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 C(M)IT): 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 C(M)IT): 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 C(M)IT): 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} for MIT is <1. This value indicates that bioaccumulation of MIT will be minimal. QSAR estimated BCF_{fish} 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	*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

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

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 11: Preservatives for liquid cooling and processing systems	ACTICIDE® M 20	Harmful microorganisms	SL-Water soluble concentrate	20 % MIT	Automated dosing system	Continuous or shock dosing	Continuous: n.a. Shock: 12 hours	5.0 mg a.s./L	NA	NA	Primary exposure occurs during dosing of the biocidal product into cooling/ processing water

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

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);	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 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);	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 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

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 4.1-02	[redacted]	2007	Determination of 5-Chloro-2-methyl-4-isothiazolin-3-one (CIT) in biocides as an impurity; [redacted] Non- GLP Unpublished	Y	Thor 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] 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; pages: 006-024;	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
			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
III-A 6.1.5-01/1	[redacted]	2000	Sensitization Study of Acticide SR 3267 in Guinea Pig Maximization Test According	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
			to Magnusson and Kligman; [redacted] GLP; Unpublished		
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] [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 6.4.1-01	[redacted]	2002	Repeated Dose 90-Day Oral Toxicity Study of ACTICIDE M 50 in Rats; [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 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; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.7-	[redacted]	1994	24-Month Drinking Water	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	[redacted]		Chronic/Oncogenic study in rats; [redacted] GLP; Unpublished		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
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;	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
			Non-GLP; Published		
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 7.1.2.2.1-02	[redacted]	2007	The determination of the degradation of 2-Methyl-2H-isothiazol-3-one (MIT, CAS * 2682-20-4) in freshwater (OECD guideline 309); [redacted] GLP Unpublished	Y	Thor GmbH
III-A	[redacted]	2002	ACTICIDE 14 - Estimation of the	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
7.1.3-02			Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC); [redacted] GLP; Unpublished		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] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.1.3-01	[redacted]	1999	ACTICIDE SR 3267: Algal Toxicity, Pseudokirchneriella subcapitata, 96 h; [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 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 (MIT, applied as aqueous formulation ACTICIDE M20) on earthworm (Eisenia fetida); [redacted] GLP; Unpublished	No	Thor GmbH
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	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]		Determine the Effects on Seedling, Emergence and Growth of Terrestrial Plants; [redacted] GLP; Unpublished		
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] GLP;Unpublished	Y	Thor GmbH
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);	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 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; [redacted] GLP; Unpublished	Y	Thor GmbH
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]	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]		[redacted] GLP; Unpublished		
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