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

Evaluation of active substances

Assessment Report

2-Methylisothiazol-3(2H)-one (MIT)

Product-type 13
(Metalworking-fluid preservative)

November 2014

Slovenia

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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(2H)-one as product-type 13 metalworking-fluid preservative carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

2-Methylisothiazol-3(2H)-one (CAS no. 2682-20-4) was notified as an existing active substance, by Rohm and Haas Europe Trading ApS, a subsidiary of The Dow Chemical Company (hereafter referred to Rohm and Haas) and Thor GmbH, hereafter referred to as the applicants, in product-type 13.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

In accordance with the provisions of Article 7(1) of that Regulation, Slovenia was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicants. The deadline for submission of a complete dossier for 2-methylisothiazol-3(2H)-one as an active substance in Product Type 13 was 31 July 2007, in accordance with Annex V of Regulation (EC) No 1451/2007.

On 9 July 2007 and 30 July 2007, SI competent authorities received dossiers from the applicants. The Rapporteur Member State accepted the dossiers as complete for the purpose of the evaluation on 31 August 2008.

On 11 April 2012, the Rapporteur Member State submitted to the Commission 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 13, 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 this assessment report, which is available from the Agency web-site 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

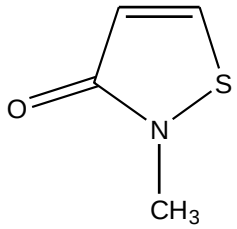
[1] Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

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

CAS-No.	2682-20-4
EINECS-No.	220-239-6
Other No. (CIPAC, ELINCS)	ENCS No 5-5235
IUPAC Name	2-methylisothiazol-3(2*H*)-one
Common name, synonyms	MIT, MI, methylisothiazolinone, 2-methyl-4-isothiazoline-3-one, 2-Methyl-2*H*-isothiazol-3-one
Molecular formula	C_4H_5NOS
Structural formula	
Molecular weight (g/mol)	115.16

The active substance is manufactured by two applicants: Thor GmbH and Rohm and Haas. The active substance as manufactured from Rohm and Haas source is a solid technical grade active substance and from Thor GmbH source a technical concentrate (TK), 50 % MIT in water solution. Equivalence of both sources of active substance as manufactured according the criteria from TNsG on the assessment of technical equivalence was ascertained as there is a single assessment report, a single LOEP and a single set of specific provisions for the Union list of approved active substances. Substances from both sources are considered to have equivalent toxicity profile concerning the Tier II evaluation and both sources are reference source. The minimum purity of 950 g/kg is supported by the analytical data (5-batch analysis) and it has been used in most of the toxicity and ecotoxicity tests in dossiers of Thor GmbH. A higher minimum purity, 980 g/kg, is supported by the 5-batch analysis and it has been used in most of the toxicity and ecotoxicity studies in the dossier of the Rohm and Haas. Both specifications have been accepted and the minimum purity of 950 g/kg shall apply for MIT.

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.

Rohm and Haas has acceptably validated analytical methods of MIT in soil, water, sediment, air and simulated food (acetic acid, water+ethanol, olive oil). The limits of quantification were 0.05 µg/g in soil and sediments, 150 µg/m^3 in air, 0.02 µg/l in water and the limit of detection was 0.05 µg/l in simulated foods.

Thor GmbH 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 Thor GmbH was accepted based on the properties and behaviour of the substance (DT_{50} < 3 days).

2.1.2. Intended Uses and Efficacy

MIT is intended to be used in professional applications in order to preserve the metalworking-fluid systems. These systems include but are not limited to the emulsifiable and water soluble metalworking fluids, metal cleaners, and water-based hydraulic fluids. The most common organisms to be controlled in these systems are microorganisms, bacteria and fungi. Microbial growth in the recirculating fluid may result in deterioration of the fluid and loss of performance features such as lubricity, emulsion stability, cooling properties, tool life, and ultimately final product quality.

The assessment of the biocidal activity of the active substance was based on the variety of standard laboratory studies including minimum inhibitory concentration and multiple challenge efficacy tests as well as field trials. It was concluded that MIT has a sufficient level of efficacy against target microorganisms at a concentration of 250 ppm. Although the concentration of MIT required to inhibit and subsequently kill microorganisms is dependent upon the species of microorganism to be controlled, contact time as well as the amount of contamination in the system, it was demonstrated that at 250 ppm MIT based biocidal products in relation to the Product Type 13 are efficacious and can act as a bactericide and fungicide.

The action of MIT against target organisms is based on a two steps mechanism which involves rapid inhibition of growth and metabolism followed by irreversible cell damage resulting in loss of viability. Critical physiological functions such as growth, respiration (oxygen consumption), and energy generation (ATP synthesis) are disrupted and cell death results from the destruction of protein thiols and production of free radicals. The latter are likely a key contributor to the cidal mechanism of MIT. Overall, the higher the concentration of a biocide, the shorter the contact time required for more complete kill. This unique mechanism results in the broad spectrum of activity of MIT biocide.

Since MIT affects a variety of metabolic processes within the cell, developing resistance to multiple targets simultaneously by microorganisms is very difficult. Furthermore, cells have to expend significant amounts of energy to repair and modify the various MIT targets and repair the damage from the radicals while their overall metabolic processes and energy systems are being shut down. Only one published report of low level microbial resistance attributed to the MIT active ingredient from a laboratory adapted strain exists in the literature.

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

A harmonised classification for 2-methylisothiazol-3(2H)-one is not available and the active substance is not listed in Annex VI of the Regulation (EC) No 1272/2008. A CLH dossier is in the procedure and will be submit to ECHA by the end of 2014.

The proposed classification and labelling for 2-methylisothiazol-3(2H)-one according to Regulation (EC) No 1272/2008 (CLP Regulation) is:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox. 3 (oral); H301 Acute Tox. 3 (dermal); H311 Acute Tox. 2 (inhalation); H330 Skin corr. 1B; H314 Skin sens. 1A; H317 STOT Single 3; H335 Aquatic Acute 1; H400 Aquatic Chronic 1; H410
Labelling	
Pictograms	GHS05 GHS06 GHS09

Signal Word	Danger
Hazard Statement Codes	H301; Toxic if swallowed. H311; Toxic in contact with skin. H330; Fatal if inhaled. H314; Causes severe skin burns and eye damage. H317; May cause an allergic skin reaction. H335; May cause respiratory irritation. H410; Very toxic to aquatic organisms with long lasting effects.
Specific Concentration limits, M-Factors	SCL ≥ 0.06 % M=10 (Aquatic acute 1) M=1 (Aquatic chronic 1)
Justification for the proposal	
H301: Based on an oral LD_{50} 120 mg MIT/kg bw, rat (females). H311: Based on a dermal LD_{50} 242 mg MIT/kg bw, rat. H314: Based on the corrosive effects observed in rabbits exposed to MIT for 3 minutes, 1 hour and 4 hours and corrosiveness in human skin epidermal construct. H317: Based on the effects observed in local lymph node assay, Magnusson-Klingmann skin sensitization test and supportive studies (Buehler test, open epicutaneous test and human patch tests). H335: Based on results from an acute inhalation toxicity study in rats, supported by and an upper airway irritation test in rats. H400: Based the 24 hours E_rC_{50} of 0.0695 mg/l from the *Skeletonema costatum* study. H410: Based the 24 hours E_rC_{10} of 0.024 mg/l from the *Pseudokierchneriella subcapiata* study and the substance failing the thresholds to be considered ready biodegradable. Simulation tests show rapid primary biodegradation of MIT in the environment to metabolites which are demonstrated or expected to be less toxic than MIT. However, ultimate biodegradation of MIT could not be demonstrated. According to Regulation (EC) No 1272/2008, primary biodegradation data can be used to justify a non-chronic classification of the parent substance if the degradation products shall not be classified as hazardous to the aquatic environment (one of the Acute or Chronic Categories). This at least requires unambiguous identification of all relevant metabolites. Definitive identification of all metabolites reaching >10% in aquatic biodegradation studies is required for an overall conclusion.	

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification and effects assessment

Absorption, distribution, metabolism and excretion

A first toxicokinetic study in rats, gavaged with 5 and 50 mg/kg bw ^{14}C-labelled MIT, indicated that 67-73 % of the low dose and 55-58 % of the high dose were absorbed in males and females, respectively, based on the radioactivity detected in urine, cage wash and tissues. In a second toxicokinetic study on bile-cannulated female rats that were administered 50 mg/kg bw ^{14}C-labelled MIT and 53 % was absorbed, when considering the radioactivity recovered in the urine and cage wash. In a third study rats received 50 mg/kg bw ^{14}C-labelled MIT and 67-69 % were absorbed in males and females as indicated by the radioactivity recovered from the urine, cage wash, cage debris and tissues. The lower absorption value 53 %, as determined in the bile cannulated rats and confirmed in another toxicokinetic study, will be used for MIT.
MIT is widely distributed in the tissues with higher values detected in the blood and that might account for high levels in the highly vascularized tissues. There is no evidence that MIT would accumulate in the body.
Metabolism of MIT in rats is extensive; 23 and 12 metabolites (detected in different dossiers)

were observed in the urine and feces of exposed animals. Parent compound was not detected in the urine, bile or feces of treated rats. As shown in two studies major urine metabolite is N-methyl malonamic acid (NMMA) (21-23 % of the dose) and 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl propionamide (10-23 % of the dose) (range from different dossiers). Twenty radioactive components were observed in the bile in low amounts, each accounting for less than 5 % of the dose, with glutathion conjugate of 3-thiomethyl-N-methyl-propionamide accounting for 4.9 % of the dose. The proposed main metabolic pathway of MIT consists of oxidative and reductive cleavage in Phase I, followed by conjugation with mercapturic acid in Phase II.
MIT is rapidly excreted from the rat. The main elimination route from the body is urine (53-70 % in 24 hours were observed in different dossiers), while feces (21-37 %) and bile (29 %) excretion are also important for elimination of MIT. The elimination half-life of ^{14}C-labelled MIT form plasma is 3.2-3.9 h at 5 mg/kg bw and 5.1-6.2 h at 50 mg/kg bw.
Based on *in vitro* dermal absorption study with various concentrations of MIT in water on human epidermis, dermal absorption value of 67 % was determined for MIT preserved products and used for the risk assessment. 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.

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.

Irritation, corrosivity and skin sensitization

MIT is considered to be corrosive to skin and eyes. It is irritant to respiratory tract. MIT is a skin sensitizer. Regarding sensitizing potential of MIT specific concentration limit ≥ 0.06 % for classification H317 (May cause an allergic skin reaction) is proposed.

Repeated dose toxicity

MIT was administered to rats by gavage for 28 and 90 days and via drinking water for 90 days. Dogs were also exposed to MIT through daily diet for 90 days. In rat and dog studies reduced food or/and water consumption were observed, presumably due to palatability problems, and consequently reduced body weight gain. In 90 days rat gavage study increased spleen weight was observed in males in the absence of histopathological findings.
The lowest NOAEL derived in the repeated dose studies is 10 mg/kg bw/day in dietary exposed dogs (90 days study). Decreased food consumption and body weight gain was observed at LOAEL, 41 mg/kg bw/day.
The 90 days dietary dog study was selected for the risk assessment of systemic effects.
Dermal and inhalation repeated dose studies were not performed with MIT. However, the applicant has submitted studies with the mixture of 5-chloro-2-methyl-2*H*-isothiazolin-3-one with MIT, CMIT:MIT (3:1), that is considered to be more toxic compared to MIT alone. These studies were submitted to demonstrate that systemic effects would be observed at levels exceeding doses that induce local effects at site of first contact.
Three months inhalation toxicity study in rats was performed with CMIT/MIT (3:1). NOAEC 0.34 mg/m^3 was derived based on slight rhinitis observed at LOAEC 1.15 mg/m^3. NOAEC for CMIT/MIT (3:1) was used in the risk assessment of local inhalation effects only to demonstrate that inhalation exposure to MIT will not induce adverse effects after repeated inhalation exposure. The use of NOAEC represents the worst case reference value for MIT since CMIT/MIT is considered to be more toxic than MIT alone.

Genotoxicity

MIT produced no evidence of genotoxicity when tested in the battery of *in vitro* and *in vivo* tests.

Chronic toxicity/carcinogenicity

Chronic toxicity and carcinogenicity potential of MIT has not been tested. Waiving of a long-term study has been justified by the applicant based on the existing information on toxic profile of MIT and genotoxicity of MIT.
Common findings in repeated dose and reprotoxicity studies are decreased food consumption and decreased body weight gain. In teratogenicity studies in rats and rabbits effects of gastric irritation were observed after exposure to MIT by gavage. Except increased spleen weight, observed in 90 days gavage rat study, no signs of true systemic toxicity were observed in treated animals. Additionally, MIT is rapidly metabolised and excreted and there is no indication that it or its metabolites would accumulate in the body. Furthermore, MIT is not genotoxic, neither *in vitro*, nor *in vivo*. Besides that in reproductive toxicity studies and repeated dose studies no evidence was observed suggesting endocrine disrupting properties of MIT. Potential tumour promoting effects caused by chronic tissue irritation would only be relevant if long-term exposure to concentrations that induce local effects would have occurred.
The probable lack of carcinogenicity of MIT can be supported by consideration of chronic studies (oral and dermal) performed on the mixture CMIT:MIT (3:1). Neither of these carcinogenicity studies indicated a carcinogenic potential.

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-breednig 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).

Human data

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 is determined and proposed as a specific concentration limit for classification.
In open literature several reports have been published on allergic reactions following MIT exposure indicating skin sensitizing potential in humans.

Health hazard of the representative products

Two representative products containing MIT, Kordek™573F (containing 50 % MIT) and ACTICIDE® M 20 S (containing 20 % MIT), were evaluated.
Kordek™573F is acutely toxic after inhalation and harmful if swallowed and in contact with skin. It is corrosive to skin and eyes, a respiratory irritant and a skin sensitizer.
Acute studies of ACTICIDE® M 20 S with exception of skin sensitization studies were conducted on MIT formulation containing 10 % active substance. Therefore concentrations triggering classification of mixtures were considered (Regulation 1272/2008) for ACTICIDE® M 20 S. If more conservative classification would be required for 10 % MIT formulation, based on study result, this classification was proposed for ACTICIDE® M 20 S. For classification of ACTICIDE® M 20 S regarding acute toxicity after inhalation the inhalation toxicity study with the 50 % MIT formulation (Doc IIIA 1.6.3-1) was considered more appropriate than applying the concentration trigger. Thereafter, ACTICIDE® M 20 S is acutely toxic by inhalation, it is harmful if swallowed and in contact with skin. It is corrosive to skin and eyes, a respiratory irritant and a sensitizer by skin contact.

Critical endpoints

In conclusion, the critical toxic effects associated with MIT are corrosion and irritation at the site of first contact, including skin, eyes, intestinal and respiratory tract, and sensitization after repeated skin contact.

Critical NOAEL/NOAEC for MIT and derivation of AEL and AEC

Due to local effects at contact site it is not possible to extrapolate between the routes of exposure and therefore route-specific risk assessment should be conducted.

Inter- and Intra-species variability

According to Risk Characterisation for local effects and sensitisation (draft, 15 May 2013) assessment factors for local AEC can be reduced. To derive an inhalation reference AEC the assessment factor 2.5 for interspecies variability and 3.2 for intraspecies variability in toxicodynamic will be considered.
For systemic toxicity default assessment factor 100 was used, 10 for interspecies and 10 for intraspecies variation.

Route to route extrapolation

Due to corrosive nature of MIT, toxicity is observed locally. Exposure to MIT is expected by the dermal and inhalation route. Therefore no no route-to-route extrapolation is appropriate for this risk assessment.

Derivation of systemic AEL

Local effects are critical effects observed in toxicity studies performed with MIT. Even though the systemic risk assessment should be conducted by default.
Several repeated dose toxicity studies were performed with MIT. In most studies reduced food consumption and body weight gain was observed. In those studies where MIT was applied by gavage signs of gastric iritation were observed in exposed animals. Reduced food concumption, water consumption and consequently decrease in body weight gain could have

been the result of palatability problem in studies where the animals were exposed to MIT in diet or drinking water. Reduced food consumption and body weight gain was also observed in animals that received MIT by gavage and probably suffered from stomach irritation. However, we can not prove that observed systemic effects are secondary to the local toxicity of MIT and not primary effects. Therefore the lowest NOAEL 10 mg/kg bw/day will be used to derive systemic AEL for MIT.
Systemic acute and medium-term AEL will be derived from NOAEL 10 mg/kg bw/day determined in the 90 days dog study using the correction factor 53 % for oral absorption and default assessment factor 100 for inter- and intraspecies differences in toxicokinetic and toxicodynamic.

Acute, medium-term AEL = 10 mg/kg bw/day ×0.53/ 100 = **0.053 mg/kg bw/day**

Because no chronic toxicity study with MIT is available, the same NOAEL value will be used to derive the long-term AEL as was for derivation of acute and medium-term AEL with the additional assessment factor 2 for extrapolation of study duration, from sub-chronic to chronic.

Long-term AEL = 10 mg/kg bw/day × 0.53/ (100 × 2) = **0.027 mg/kg bw/day**

Derivation of acceptable external concentration (AEC)

Dermal route
The most critical local dermal effect of MIT is skin sensitization. NOAEC for skin sensitisation was determined to be 0.06 % (600 ppm) MIT as follows from the skin sensitization study in human volunteers where the concentrations up to and including 600 ppm did not induce skin sensitization in humans in studies submitted by the applicants.
In order to take into account the skin sensitizing potential of MIT, the specific concentration limit for skin sensitization (0.06 %) will be compared to the potential exposure values in a semi-quantitative risk assessment.

Inhalation route
According to proposed pattern of use neither respirable particles or droplets nor aerosols will be formed during the use of Kordek^{TM}573F and ACTICIDE® M 20 S and inhalation exposure is considered to be very low.
Repeated inhalation toxicity study was not conducted with MIT but with the combination of CMIT:MIT (3:1) in 90 days rat study. This study demonstrated that after sub-chronic inhalation exposure signs of respiratory irritation occur in the absence of systemic effects. Because no data exist, inhalation AEC cannot be set for MIT, but it can be derived from CMIT/MIT (3:1). For CMIT/MIT higher bioavailability is expected after inhalation exposure. In addition, it is more toxic by oral and dermal route and RD_{50} for CMIT/MIT is also lower compared to MIT. Therefore it is assumed that repeated exposure to MIT would result in comparable NOAEC/LOAEC values. Based on NOAEC 0.34 mg a.s./m^3 from the CMIT/MIT (3:1) 90 days rat study and assessment factor 2.5 for interspecies difference in toxicodynamic and 3.2 for intraspecies difference in toxicodynamic an inhalation acute and medium- term AEC can be derived. Due to irritant and corrosive properties the assessment factor for toxicokinetic intraspecies difference can be reduced to 1.

Acute, medium-term $AEC_{inhalation}$= 0.34 mg a.s./m^3/(2.5 ×3.2) = **0.043mg a.s./m^3**

For derivation of long-term AEC additional safety factor 2 should be applied for extrapolation of repeated inhalation toxicity study duration from sub-chronic to chronic.

Long-term $AEC_{inhalation}$= 0.34 mg a.s./m^3/(2.5 ×3.2 × 2) = **0.021 mg a.s./m^3**

Based on CMIT/MIT (3:1) NOAEC an acute and medium-term $AEC_{inhalation}$ 0.043 mg /m^3 and long-term $AEC_{inhalation}$ 0.021 mg /m^3 were proposed. Even though inhalation AEC values are considered conservative, they were derived in order to demonstrate the safe use of MIT in

MWF. Since MIT is of lower or comparable toxicity than CMIT/MIT it seems reasonable to use this value in the risk assessment for local inhalation effects.

2.2.1.2. Exposure assessment

The exposure assessment was carried out for proposed uses of two MWF preservative biocidal formulations, Kordek™573F (containing 50 % MIT) and ACTICIDE® M 20 S (containing 20 % MIT). The biocidal products under evaluation will only be used by professionals.

Relevant exposure paths

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

1. Mixing and Loading; metalworking concentrate (containing MIT) is diluted and added to the sump or the biocidal product is added directly to the sump,
2. Application; the metalworking process involves operating the machines, handling objects wetted with MWF, and other daily tasks,
3. Post application (includes disposal); includes sump maintenance and fluid monitoring, disposal and recycling.

The main routes of exposure to MIT are presented in the following Table 2.1.

Table 2.1 Main path of human exposure to MIT

Exposure path	Industrial use	Professional use[a]	General public[b]	Via the environment[c]
Inhalation	No	Yes	No	No
Dermal	No	Yes	No	No
Oral	No	No	No	No

[a] includes professional operators and secondary exposure to contaminated articles

[b] secondary exposure

[c] From TNsG on Human Exposure, 2007: 'Exposure via environment is an element of secondary exposure. It includes bystanders and consumers, including children, who are inadvertently exposed to biocides by inhalation of plumes drifting off-site and ingesting contaminated food. These scenarios are not considered to be relevant in this case.'

Main pathway of primary exposure to MIT is by dermal route. Oral exposure is not considered relevant route of exposure.

For each exposure scenario, Tier 1 exposure estimates are provided and since Tier 1 assessment leads to unacceptable risks, Tier 2 assessment has been developed assuming appropriate PPE and/or risk mitigation measures and for the application phase further refinement.

MIT is proposed to be classified as a skin, eye and respiratory irritant and a skin sensitizer. The most critical local effect is skin sensitization, with the proposed SCL ≥ 0.06 %. Therefore any contact with the biocidal products containing 20 or 50 % MIT should be prevented by the RMM for high hazard class chemicals, including semi-automated or automated mixing and loading of MIT into MWF and the use of impermeable coverall, protective gloves, boots and face shield during handling these products. The concentration of MIT in MWF is below the SCL for skin sensitization and that is why no adverse local effects are expected after handling MIT

preserved MWF. Besides that the use of impermeable coverall and gloves is proposed also during application tasks.

Mixing and loading phase

MIT is added to the MWF to preserve it. The mixing and loading tasks involve introduction of the biocidal product into the metalworking fluid sump and may be conducted by automation or manually. Due to systemic toxicity and severe local effects that are expected to occur through the contact of 50 % MIT with the skin, any dermal contact with the biocidal product should be prevented, what should be achieved by technical and organizational RMM for high risk chemicals and appropriate PPE. That is why the manual mixing and loading is considered not to be acceptable and will not be evaluated further in the risk characterization.

Exposure to MIT in MWF was estimated for semi-automated introduction of the biocidal product into MWF as a worst case scenario, taking into account that mixing and loading takes place once per 1 to 6 weeks, for 10 minutes.

Application phase

The application of MWF involves tool setting, metalworking, dismantling tools, handling worked pieces, cleaning of tools and surfaces. During metalworking (1 hour per day) the use of protective gloves can be a safety hazard, therefore it was assumed in the exposure scenario that no gloves, but impermeable coverall is worn during these phase. To ensure safe use coverall and gloves should be worn during metalworking tasks, except during machine work where the use of gloves is not a common practice due to dexterity and safety reasons. However, daily task of the operator is application of the MWF (metalworking and other tasks). Mixing and loading of the biocidal product into the sump, sump maintenance and fluid monitoring take place only occasionally.

Post-application phase

Post-application of MWF includes sump maintenance, fluid monitoring, recycling of the fluid and cleaning the equipment and the tools. Post-application tasks can be performed by operators involved in the application of the MWF or other professionals.
Sump maintenance occurs once a month and takes 4 hours, while fluid monitoring is performed once a week and takes 10 minutes. The exposure during these tasks is lower compared to the exposure during the application phase. Besides that, post-application tasks are performed with low frequency. Therefore, the risk for the operator from exposure to MIT during post-application tasks was not assessed separately, but is considered to be acceptable as it is covered with the risk assessment for the operator during the application phase. Additionally, operators performing post-application tasks will be exposed to concentrations of MIT below the specific concentration limit for skin sensitization and are expected to wear appropriate PPE (protective gloves and impermeable coverall) during these tasks.

Combined exposure

The combined exposure has been estimated considering the professional conducting several tasks in one day. The worker is assumed to load the biocidal product into the sump, to do the metalworking and post-application tasks (fluid monitoring, cleaning) all during one shift.

Table 2.2 Summary of total estimated exposure to Kordek™ 573F (50 % MIT)

Exposure Scenario (indicate duration)		Estimated Internal Exposure			
		estimated oral uptake [mg/kg b.w/day]	estimated inhalation uptake [mg/kg b.w/day]	estimated dermal uptake [mg/kg b.w/day]	estimated total uptake [mg/kg b.w/day]
Tier 1 (no PPE) 100 % clothing penetration,100 % dermal uptake mixing, 67 % dermal uptake application)	Semi-automated loading (10 min) Application (1hr metalworking+7 hrs other tasks) And/or post-application tasks	/	1.38×10^{-5}	1.75×10^{-1}	1.75×10^{-1}
Tier 2 (gloves for each task except metalworking, impermeable coveralls, face shield during mixing and loading) 5 % clothing penetration 10 % glove penetration 100 % dermal uptake mixing, 67 % dermal uptake application)		/	1.38×10^{-5}	5.07×10^{-2}	5.07×10^{-2}
Tier 2 refinement (gloves for each task except metalworking, impermeable coveralls, washing hands after machine working, face shield during mixing and loading) 5 % clothing penetration 10 % glove penetration 100 % dermal uptake mixing, 67 % dermal uptake application		/	1.38×10^{-5}	1.72×10^{-2}	1.72×10^{-2}

Table 2.3 Summary of total estimated exposure to ACTICIDE® (20 % MIT)

Exposure Scenario (indicate duration)		Estimated Internal Exposure			
		estimated oral uptake [mg/kg b.w/day]	estimated inhalation uptake [mg/kg b.w/day]	estimated dermal uptake [mg/kg b.w/day]	estimated total uptake [mg/kg b.w/day]
Tier 1 (no PPE) 100 % clothing penetration 67 % dermal uptake application)	Semi-automated loading (10 min) Application (1hr metalworking+7 hrs other tasks) And/or post-application tasks	/	1.38×10^{-5}	1.66×10^{-1}	1.66×10^{-1}
Tier 2 (gloves for each task except metalworking, impermeable coveralls, face shield during mixing and loading) 5 % clothing penetration 10 % glove penetration 100 % dermal uptake mixing, 67 % dermal uptake application		/	1.38×10^{-5}	5.02×10^{-2}	5.02×10^{-2}
Tier 2 refinement (gloves for each task except metalworking, Impermeable coveralls, washing hands after machine working, face shield during mixing and loading) 5 % clothing penetration 10 % glove penetration 100 % dermal uptake mixing, 67 % dermal uptake application		/	1.38×10^{-5}	1.67×10^{-2}	1.67×10^{-2}

Secondary exposure

Other potential secondary exposure scenarios include cleaning surfaces and equipment, collecting shavings (swarfs), used fluid and empty drumps for recycling or disposal and transferring worked pieces to storage. Potential exposure to MIT from these tasks is anticipated to be covered by other tasks during application phase.

Exposure of non-professionals

As the biocidal product is not intended for non-professional use, exposure of the general public via primary respectively secondary exposure is not considered for this assessment.

2.2.1.3. Risk characterisation

Primary exposure

Quantitative risk assessment was performed for both, systemic and local effects (sensitization, irritation), by comparing estimated exposure with relevant reference value (AELs or AECs). The ratio Exposure/AEL or Exposure/AEC < 1 means that the risk from a certain use is acceptable.
In addition to AEL approach the margin of exposure (MOE) approach will also be used for the risk characterization after estimated exposure to MIT. The MOE approach compares the critical NOAEL with the estimated exposure. The ratio NOAEL/Exposure below the reference MOE for systemic and local effects indicates that is the risk of exposure to MIT is acceptable.

Primary exposure from use of Kordek^{TM}573F

Kordek^{TM}573F is mostly introduced into MWF automatically in closed system or semi-automatically via connection pipes. The quantitative risk assessment for systemic effects has been performed for semi-automated loading and it was shown that the operator exposure during this phase of use of the biocidal product is below the reference value for MIT (3 % $AEL_{long\text{-}term}$). The risk for local dermal effects during mixing and loading, namely skin sensitization as the most critical effect, was estimated qualitatively and was considered to be acceptable for the operator if organizational and technical RMM for high hazard class chemicals are in place and the appropriate PPE is used by professionals performing the loading of biocidal product. Users of Kordek^{TM}573F will be professionals only and the CLP and RMMs (including use of PPE) are considered to efficiently prevent the occurrence of the event of skin contact with MIT during mixing and loading and thereby protect from local and systemic effects. Besides that, any toxicity of MIT will be expressed as an immediate contact event and so, it is highly unlikely that exposure will be prolonged, as exposure personnel will remove themselves from the vicinity of exposure.
Exposure from daily application task (1 h metalworking and 7 hrs other tasks) with MWF, preserved by MIT, results in 61 % of the systemic long-term AEL, if protective coverall and gloves are used (except during metalworking) to reduce the systemic exposure to an acceptable level. MOE from application task is 610 (reference MOE 200 when considering oral absorption 53 %). Local dermal exposure from application of MWF was assessed semi-quantitatively and was considered acceptable. Additionally, the concentration of MIT in MWF during the application phase is below the concentration that would lead to local effects. Local inhalation exposure accounts for 0.06 % of $AEC_{long\text{-}term}$ derived for CMIT/MIT (3:1). Presented exposure assessment is based on indicative exposure values and an assumption that operator will wash hands during the working day, after metalworking and before putting on protective gloves. Post-application tasks, fluid monitoring and sump maintenance, are performed once per week for 10 minutes and once per months for 4 hours, respectively. The exposure to MIT during post-application phase is lower compared to the application tasks and is performed infrequently. Therefore the risk for post-application tasks was not assessed separately since the operator exposure during the application tasks is acceptable and therefore the operator exposure during post-application tasks would be acceptable as well.

Primary exposure from use of ACTICIDE® M 20 S

For ACTICIDE® M 20 S quantitative risk assessment for systemic effects was performed for manual, semi-automated and fully automated mixing and loading for the same reasons as stated for Kordek™573F. Due to corrosive, irritant and sensitizing properties of ACTICIDE® M 20 the manual loading is not acceptable. The quantitative risk assessment for systemic effects has been performed for semi-automated loading and it was shown that the operator exposure during this phase of use of the biocidal product is below the reference value for MIT (1 % $AEL_{long\text{-}erm}$). The risk for local dermal effects, namely skin sensitization as the most critical effect, was estimated semi-quantitatively and was considered to be acceptable for the operator if organizational and technical RMM for high hazard class chemicals are in place and the appropriate PPE is used by professionals performing the loading of biocidal product. Users of ACTICIDE® M 20 S will be professionals only therefore RMMs (including use of PPE) are considered to efficiently reduce the occurrence of the event of skin contact with MIT during mixing and loading and thereby protect from local and systemic effects. However, exposure and quantitative risk assessment for professionals were carried out for daily application task of MWF (1 h metalworking and 7 hrs other tasks). Results of quantitative risk assessment are the same as for Kordek™573F since the same use is proposed for both formulations. This means that systemic exposure to MIT accounts for 61 % of the systemic AEL and inhalation exposure for 0.06 % when compared to the $AEC_{long\text{-}term}$ for CMIT/MIT Presented exposure assessment is based on an assumption that operator will wash hands during the working day, presumably after metalworking and before putting on protective gloves, and wear coverall and protective gloves during all tasks except machine work. If washing hands after metalworking and before putting on protective gloves is considered, systemic exposure is reduced twice and local dermal exposure more than 30 times. Local dermal exposure from application of MWF was assessed semi-quantitatively and was considered acceptable. Additionally, the concentration of MIT during the application phase is below the concentration that would lead to local effects. Post-application tasks, fluid monitoring and sump maintenance, are performed once per week for 10 minutes and once per months for 4 hours, respectively. The exposure to MIT during post application phase is lower compared to the application tasks and is performed infrequently. Therefore the risk for post-application tasks was not assessed separately since the operator exposure during the application tasks is acceptable and therefore the operator exposure during post-application tasks would be acceptable as well.

Secondary (indirect) exposure as a result of use

Risk for secondary exposure to MIT when transferring of machined metal from lathe to storage area and collecting shavings (swarfs) is covered by the risk assessment for the operator and is considered acceptable. Bystander exposure to metalworking fluids containing MIT is also considered irrelevant since operations are conducted in closed buildings with restricted access. Consumer exposure to metalworking fluids containing MIT is not relevant since these products are recommended and sold for professional use only.

Combined exposure

The combined exposure (total exposure (via all exposure routes) arising from individual tasks through different phases of use) scenario involves one operator conducting several tasks in the same work shift. Risk from combined exposure to MIT is considered acceptable when Kordek™573F and ACTICIDE® M 20 S are used according the instructions, respecting organizational and technical RMM for high hazard class chemicals and using the proposed appropriate PPE.

Overall assessment of the risk for the use of the active substance in biocidal products

To conclude, the performed risk assessment indicates that proposed use of MIT as PT13, formulated in Kordek™573F and ACTICIDE® M 20 S, will not result in unacceptable risk for systemic or local effects for primary exposed professionals. To ensure safe use of MIT organizational and technical RMM for high hazard category chemical must be applied and the

appropriate PPE must be worn by professionals handling respective biocidal products.

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. Thus the primary route of dissipation in the environment is biological. The Technical Meeting TMIV08 (December 2008) agreed that identification of photodegradation products can be waived in the specific case of CMIT and MIT, because biodegradation is faster than photodegradation. There is no need for further work to confirm the identity of photodegradation products. In the troposphere, the calculated radical catalyzed degradation of MIT and its metabolites is very rapid resulting in half-life of 16.6 hours for the parent and 31.8 hours or less for metabolites.

Biodegradation

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

Adsorption

The available studies indicate a low adsorption potential of MIT (K_{OC} 6.4-10 l/kg). In sewage

treatment plants and surface waters, MIT will be predominantly present in the water phase. The substance will not accumulate in sludge or sediments. MIT may have a potential for leaching in soil, but the rapid biodegradation of the substance in soil (half-life < 0.5 day) indicates that the risk for groundwater can be considered very low.

Bioconcentration

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

2.2.2.2. Effects assessment

Aquatic toxicity

Acute and long-term studies are available for fish, invertebrates and algae. Within trophic levels differences between toxicity to freshwater species and toxicity to saltwater species are less than a factor 10. As agreed in TMI-13 the lowest value of either the geometric mean value of the 24h $E_rC_{10,ini}$ for the freshwater species *Pseudokierchneriella subcapitata* or the single reliable 24h $E_rC_{10,ini}$ for the saltwater species *Skleletonema 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 *Pseudokierchneriella 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 *Skleletonema 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)

2.2.2.3. 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.

2.2.2.4. Exposure assessment

The industrial use/service life stage occurs when the metalworking fluid cools and/or lubricates the industrial machinery. This is the stage at which MIT is required to exert its biocide effect. At the end of the lifetime of the metalworking fluid, it is then disposed of, together with any MIT remaining. As no product specific exposure data are available, the assessment of environmental exposure was based on exposure scenarios assumptions for "use" and "disposal" stages of the product. Losses during the "industrial use" phase are negligible compared to losses at the "disposal" stage and hence only assessment of the exposure via waste water was performed. Exposure via waste water was estimated following the Environmental emission Scenario Document (ESD) for product type 13. The ESD defines two possible scenarios; for emulsifiable (water-based) metalworking fluids and soluble metalworking fluids. These scenarios estimate the emission for a waste treatment facility receiving spent metal-working fluids.
The Fraunhofer report for the refinement of the environmental emission scenario for metalworking fluids[2] concludes on the basis of recent information received from companies that the EUBEES-ESD for PT13 is not able to reflect the release of biocides from the use and waste treatment of water miscible metalworking fluids in Europe in an adequate way. More realistic Tier 2 exposure estimates were in addition calculated with refinements proposed in this report.
Four reliable DT_{50} values were available for biodegradation in water-sediment systems- A geometric mean value of 2.21 d for whole system at 12 ºC was used in the exposure estimation. For biodegradation in STP the single reliable DT_{50} value of 0.04 d (20 ºC) was used in the exposure estimation. For soil the highest DT_{50} value of 0.51 d (12 ºC) was used in the exposure estimation, since only two DT_{50} values were available.

2.2.2.5. Risk characterisation

Atmosphere

The use/disposal stage of the biocidal products as metalworking-fluid preservative is predicted to result in negligible concentrations of MIT in air. In accordance with the Technical Guidance Document a "quantitative characterization of risk relevant to biotic effects by comparison of the PECair to PNECair is not possible". However based on a qualitative assessment of the exposure following the use of the biocidal products as metalworking-fluid preservative, there is considered to be a negligible risk to the environment from atmospheric exposure. Risks relevant to abiotic effects to the atmosphere are negligible due to the expected negligible concentrations of MIT in the air.

Aquatic environment (incl. sediment)

[2] Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Chemical Risk Assessment: "Gathering of information for the refinement of the Environmental Emission Scenario for metalworking fluids (PT13) under BPD/R", Addendum 1. 31 October 2013

The Tier 1 PEC/PNEC ratio microorganisms within sewage treatment plants is above 1 for the use in emulsifiable MWF and below 1 for the use in water-soluble MWF, indicating an unacceptable risk to microorganisms within sewage treatment plants for the use in emulsifiable MWF. It has to be kept in mind, that a worst case scenario was calculated, assuming that the emulsifiable metalworking fluid still contains nearly 98% of dosed MIT at the end of service life and that the whole amount of treated volume is released to an STP in one single event. Furthermore degradation of MIT before reaching the STP is ignored. Therefore Tier 2 calculations were performed, considering a dilution factor of 100 for the dilution from the company to an external STP and a factor of relevance of 0.5. The resulting PEC/PNEC ratios are <1 for both the use in water-soluble MWF and the use in emulsifiable MWF, indicating an acceptable risk.

In Tier 1 emissions during recovery of spent metalworking fluid are identified as a potential risk to the aquatic environment. The PEC/PNEC ratio is above 1 for both the use in emulsifiable MWF and the use in soluble MWF. It has to be kept in mind that the ESD for PT13 is very conservative and that degradation processes were ignored in the calculations. Therefore Tier 2 calculations were performed, considering dilution factors of 100 for the dilution from the company to an external STP as well as the dilution from STP to the receiving river and a factor of relevance of 0.5. The resulting PEC/PNEC ratios are <1 for both the use in water-soluble MWF and the use in emulsifiable MWF, indicating an acceptable risk.

The physico-chemical properties of MIT ($logK_{OW}$ = -0.32 at pH7 and 20 ºC) and its rapid degradation in surface waters (whole system DT_{50} in water-sediment systems 0.86-4.17 days at 12 °C) suggest that the active substance is not likely to partition into sediment to a significant extent. A $PNEC_{sed}$ derived from equilibrium partitioning would be most adequate. Considering that in this case the PEC/PNEC ratio for water and sediment is similar, the risk assessment for fresh water covers that of sediments as well.

Groundwater and terrestrial environment

The Tier 1 PEC/PNEC ratio for the terrestrial compartment is above 1 for the use in emulsifiable MWF and below 1 for the use in water-soluble MWF, indicating an unacceptable risk to soil organisms from sewage sludge amendment of soil for the use in emulsifiable MWF. It has to be kept in mind that the ESD for PT13 is very conservative and that degradation processes were ignored in the calculations. Therefore Tier 2 calculations were performed, considering dilution factors of 100 for the dilution from the company to an external STP as well as the dilution from STP to the receiving river and a factor of relevance of 0.5. The resulting PEC/PNEC ratios are <1 for both the use in water-soluble MWF and the use in emulsifiable MWF, indicating an acceptable risk.

In Tier 1, the concentration in pore water (surrogate for groundwater) are < 0.1 µg/l set up for pesticides for the use of MIT as a preservative in water soluble metalworking fluids, indicating acceptable risk of leaching to groundwater. For the use of MIT as a preservative in emulsifiable metalworking fluids the trigger of 0.1 µg/l is in Tier 1 slightly exceeded.

It has to be kept in mind that the ESD for PT13 is very conservative and that degradation processes were ignored in the calculations. Therefore Tier 2 calculations were performed, considering dilution factors of 100 for the dilution from the company to an external STP as well as the dilution from STP to the receiving river and a factor of relevance of 0.5. The resulting PEC/PNEC ratios are <1 for both the use in water-soluble MWF and the use in emulsifiable MWF, indicating an acceptable risk. In Tier 2, the concentration in pore water (surrogate for groundwater) are < 0.1 µg/L set up for pesticides for the use of MIT as a preservative in water soluble metalworking fluids as well as the use of MIT as a preservative in emulsifiable metalworking fluids, indicating acceptable risks to groundwater for this use.

Risk assessment metabolites

Regarding the metabolites from the water- and water/sediment studies no quantitative risk assessment has been conducted. Based on either experimental data or QSAR estimates,

submitted by Rohm and Haas, these metabolites are several orders or magnitude less toxic than MIT and cannot be considered persistent. Therefore, it is not likely that they would pose a risk to the environment.

Cumulative exposure

Since the active substance MIT is intended to be used by several applicants in multiple biocidal products as well as in more than one PT it can be questioned if there could be an overlap in time and space. However, no agreed methodology for cumulative risk assessments exists so far.

2.2.3. 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 2-methylisothiazol-3(2H)-one in product-type 13 is specified in the BPC opinion following discussions at the meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. List of endpoints

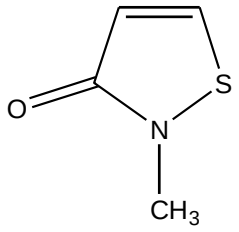
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

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 13: Metalworking-fluid preservative

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	
EC No	220-239-6	
Other substance No.	ENCS N° 5-5235	
Minimum purity of the active substance as manufactured (g/kg or g/l)	*Rohm and Haas:* 980-1000 g/kg	*Thor GmbH:* > 950 g/kg
	The sources of the substances are considered equivalent according the TNsG on the assessment of technical equivalence of substances regulated under Directive 98/8/EC. Both specifications have been accepted and the minimum purity of 950 g/kg shall apply for MIT.	
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	**<u>Impurities</u>:** CONFIDENTIAL INFORMATION	
	<u>Additives</u>: 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·m^3·mol^{-1} at 20 ºC and pH 5	*Thor GmbH:* $< 4.39 \times 10^{-5}$ Pa·m^3·mol^{-1}
Solubility in water (g/l or mg/l, state temperature)	*Rohm and Haas:* pH__5, 9____:> 1000 g/l at 20 °C	*Thor GmbH:* pH__5, 7, 9____: > 1000 g/l at 10, 20 and 30 °C pH__4.5____:> 4287.2 g/l at 20 °C
Solubility in organic solvents (in g/l or mg/l, state temperature)	*Rohm and Haas:* <u>Solubility in hexane:</u> 2.42 g/l at 30 ºC 0.93 g/l at 10 ºC <u>Solubility in ethyl acetate:</u> > 1000 g/l at 30 ºC 562.15 g/l at 10 ºC	*Thor GmbH:* 1.46 g/l in <u>n-hexane</u> at 21 °C 143.6 g/l in <u>xylene</u> at 21 °C
Stability in organic solvents used in biocidal products including relevant breakdown products	Not applicable; active substance as manufactured does not include an organic solvent.	

Partition coefficient (log P_{OW}) (state temperature)	*Rohm and Haas:* log P_{ow} = - 0.486 at 24 °C, pH not stated (not pH and T dependent)	*Thor GmbH:* pH__5____: log P_{ow} = -0.26 at 20 °C pH__7____: log P_{ow} = -0.34 at 10 °C pH__7____: log P_{ow} = -0.32 at 20 °C pH__7____: log P_{ow} = -0.34 at 30 °C pH__9____: log P_{ow} = -0.28 at 20 °C
Hydrolytic stability (DT_{50}) (state pH and temperature)	*Rohm and Haas:* In pH 5, 7, and 9 buffers (24.1 ± 0.4 °C) no significant hydrolysis of MIT was observed as the compound was stable for more than 720 hours.	*Thor GmbH:* pH 4, 7 and 9: DT_{50} >1 year (extrapolated from results of a preliminary test at 50 °C)
Dissociation constant	*Rohm and Haas:* Not applicable; MIT does not dissociate into ionic species. (Expert statement)	*Thor GmbH:* Low dissociated compound pK > 2.81 (purity = 98.5 %; conductometer method)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	*Rohm and Haas:* Neutral pH: λ_{max} at 274 nm, Abs. = 0.93203, ∈ = 7760 Acid pH: λ_{max} at 266 nm, Abs. = 0.94372, ∈ = 7950 Acid pH: λ_{max} at 212 nm, Abs. = 0.33744, ∈ = 2843 Basic pH: λ_{max} at 274 nm, Abs. = 0.93627, ∈ = 8085 Basic pH: λ_{max} at 215 nm, Abs. = 0.20294, ∈ = 1752	*Thor GmbH:* Neutral pH: λ_{max} at 273 nm, log ε = 3.88 Acid pH: λ_{max} at 273 nm, log ε = 3.88 Methanol: λ_{max} at 277 nm, log ε = 3.87
Photostability (DT_{50}) (aqueous, sunlight, state pH)	DT_{50} = 11.1 -18.2 d at pH 7 (sunlight), geometric mean 14.2 d	
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not determined.	
Flammability	*Rohm and Haas:* Not highly flammable	*Thor GmbH:* Not flammable
Explosive properties	Not explosive	
Oxidising properties	Not oxidising	

Classification and proposed labelling

with regard to physical/chemical data	-

with regard to toxicological data	**Hazard Class and Catagory**	**Hazard Statement**
	Acute Tox. 3 (oral) Acute Tox. 3 (dermal) Acute Tox. 2 (inhalation) Skin corr. 1B 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 Aquatic Chronic 1	H400; Very toxic to aquatic life H410; Very toxic to aquatic organisms with long lasting effects

* Discusion on environmental classification: Category: Aquatic Chronic 1, a final decision will be made by ECHA.

Chapter 2: Methods of Analysis

Analytical methods for the active substance

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

Analytical methods for residues

Soil (principle of method and LOQ)	*Rohm and Haas:* Solid phase extraction followed by reversed phase HPLC with UV detection (275 nm); LOQ = 0.05 µg/g of	*Thor GmbH:* Not submitted; an active substance will not be present in soil due to high mobility and fast degradation rate.

	soil or sediment.	
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.	*Thor GmbH:* HPLC/MS/MS; LOQ (limit of quantification) = 0.1 µg/l
Body fluids and tissues (principle of method and LOQ)	-	
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	*Rohm and Haas:* Extraction/dilution followed by HPLC/MS/MS analysis; Limit of detection is 0.004 mg/l ppb).	*Thor GmbH:* HPLC-MS analysis; LOQ (limit of quantification) = 0.025 µg/ml LOD (limit of detection) =0.006 µg/ml The available analytical method is suitable for the determination of MIT in the food simulants acetic acid, 10 % ethanol and olive oil.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required.	

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	*Rohm and Haas:* **53**-69 **%** at 50 mg base-eq./kg b.w. 67-73 % at 5 mg base-eq./kg b.w. (rat)	*Thor GmbH:* 67-69 % at 50 mg base-eq./kg b.w. (rat)
Rate and extent of dermal absorption:	*Rohm and Haas:* *In vitro* rat skin: 68-81 % over the range of concentrations tested (25 to 150 ppm MIT). *In vitro* human skin: 66, 62 and 67 % from an aqueous solution of MIT at concentrations of 52.2, 104 and 313 µg MIT/ml, respectively.	

	100 % for the active substance and biocidal product **67% for a preserved product**
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 and 60 min). 21-day cumulative skin irritation (humans): not irritant ≤ 500 ppm (39.5 μg/cm^2)	*Thor GmbH:* Corrosive; 0.5 ml of MIT applied undiluted (rabbit)
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 ≥0.06 %	*Thor GmbH:* Sensitizer

Acute toxicity of MIT metabolites

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

Repeated dose toxicity

Species/ target / critical effect	Rat-dog-rabbit/reduced food and/or water consumption, reduced body weight gain, increased spleen weight	
Lowest relevant oral NOAEL / LOAEL	*Rohm and Haas:* NOAEL = **9.9** and 11.1 mg a.i./kg bw/day in males and females, respectively (400 ppm); 3 months (dog, diet). LOAEL = 40.6 and 40.9 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 CMIT/MIT (3:1): 90 days NOAEL (rabbit) was not determined; LOAEL = 0.1 mg CMIT/MIT/kg bw/day (100 ppm); irritation at site of contact 30 months NOEL (mouse) = 400 ppm CMIT/MIT (3:1). There were no systemic toxic effects in this study.	
Lowest relevant inhalation NOAEL / LOAEL	*Rohm and Haas, Thor GmbH:* Test with CMIT/MIT (3:1): 90 days NOEL (rat) = **0.34 mg CMIT/MIT (3:1)/m^3** based on irritation to the respiratory tract. 90 days LOEL (rat) = 1.15 mg CMIT/MIT (3:1)/m^3, based on slight, treatment-related rhinitis. There were no systemic toxic effects in this study.	

Repeated dose toxicity of MIT metabolites

Species/ target / critical effect	Rat/-	
Lowest relevant oral NOAEL / LOAEL	*Rohm and Haas:* N-methyl malonamic acid (NMMA): 90 days NOEL (diet, rat) = 13-15 mg NMMA/kg bw/day (100-220 ppm), the highest dose tested. Malonamic acid (MA): 90 days NOEL (diet, rat) = 2.6-3.0 mg MA/kg bw/day (22-44 ppm), the highest dose tested.	*Thor GmbH:* /

Genotoxicity

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

Genotoxicity of MIT metabolites

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

Carcinogenicity

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

Reproductive toxicity

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

Neurotoxicity / Delayed neurotoxicity

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

Other toxicological studies

Rohm and Haas, Thor GmbH:

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

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

Rohm and Haas :

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

Medical data

Rohm and Haas:

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

Summary	Value	Study	Safety factor
ADI (if residues in food or feed)	n.a.	n.a.	n.a
Systemic AEL (acute and medium -term)	0.053 mg/kg bw/day	90-days dietary study (dog)	100 (53 % oral absorption)
Systemic AEL (long term*)	0.027 mg/kg bw/day	90-days dietary study (dog)	200 (53 % oral absorption)
Inhalation AEC (acute, medium)	0.043 mg/m^3	90-days inhalation study with CMIT/MIT (3:1 in rat	8
Inhalation AEC (long-term)	0.021 mg/m^3	90-days inhalation study with CMIT/MIT (3:1 in rat	16
Dermal NOAEC	0.06 % (600 ppm)	Human skin sensitization study	N/A
Drinking water limit	Not required.	N/A	N/A
ARfD (acute reference dose)	N/A		

* 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)

Professional users

PT13
Two representative formulations submitted by two applicants were assessed:
- Kordek^{TM}573F: a water based biocidal product (50 % MIT), concentration of MIT in the MWF is 0.0250 % w/w;
- Acticide M 20 S: a water based biocidal product (20 % MIT), concentration of MIT in the MWF is 0.0250 % w/w.

Operator's exposure assessment includes exposure from **mixing the biocidal product into the MWF**, **application of MWF** (tool setting, metal working, handling worked pieces, dismantling tools, cleaning tools and surfaces, transferring of machined metal from lathe to storage area assessment) and **post-application tasks** (fluid maintenance and fluid monitoring).

Exposure assessment is based on simple database models listed below:

Use phase	**Relevant model**
Mixing and loading	RISKOFDERM Toolkit (Loading liquid, partly automated)
Metalworking - machining metal tool parts	BEAT' worked example PT13 - Machining of metal parts MWF Model 1 (hand exposure)

	Other tasks at the metalworking machine	BEAT' worked example PT13 - Machining of metal parts Handling model 1 (hand exposure)
	Maintenance/cleaning	BEAT Cleaning spray equipment
	PPE: Gloves for each task except metalworking, impermeable coverall during all tasks and face shield for mixing and loading. The performed risk assessment indicates that proposed use of MIT as PT13, formulated in KordekTM573F and ACTICIDE® M 20 S, does not result in unacceptable risk for systemic and local dermal or respiratory effects for primary exposed professionals. To insure the safe use of KordekTM573F and ACTICIDE® M 20 S technical and organizational RMM for high hazard class chemicals must be applied during mixing and loading phase and the operators must wear the appropriate PPE.	
Non-professional users	Non-professional use is not envisaged.	
Indirect exposure as a result of use	Secondary exposure is not envisaged.	

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	*Thor GmbH:* No 0 % biodegradation in Closed Bottle Test

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

Route and rate of degradation in soil

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

	maximum after 22 hours	
Soil accumulation and plateau concentration	No accumulation of MIT in soil as a result of quick biodegradation.	

Adsorption/desorption

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

Fate and behaviour in air

Direct photolysis in air	*Rohm and Haas:* The phototransformation rate constant and half-life were calculated using structure activity relationship (SAR) methods. The rate constant, k, was 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 $kdeg_{air}$ = 1.00E-2 d^{-1} 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	*Thor GmbH: Daphnia magna* 21 d NOEC survival 0.55 mg/l(mm)

	0.359 mg/l(mm) 21 d NOEC (dry) weight 0.0442 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 CMIT): LD_{50} = 460.71 mg /kg bw (eq. to 64.5 mg a.i./kg bw)	-
Dietary toxicity to birds	*Rohm and Haas:* Bobwhite quail (study with CMIT): LC_0 = 10357 mg /kg (eq. to1450 mg /kg a.i.) LC_{50} = 25257 mg /kg (eq. 3536 mg /kg a.i.) Mallard Duck (study with CMIT): LC_0 = 1614 mg /kg (eq. to 226 mg /kg a.i.) LC_{50} = 6750 mg /kg (eq. to 945 mg /kg a.i.)	-
Reproductive toxicity to birds	Not available	

Effects on honeybees

Acute oral toxicity	Not available
Acute contact toxicity	Not available

Effects on other beneficial arthropods

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

Bioconcentration (Annex IIA, point 7.5)

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

Chapter 6: Other End Points

Effects on Terrestrial plants

Seedling emergence and seedling growth	*Rohm and Haas:* <u>Oilseed rape *(Brassica napus)*</u> NOEC, shoot height and weight 10 mg/kg dry soil (nom.) EC_{50}, shoot weight 36 mg/kg dry soil (nom.) <u>Red clover (*Trifolium pratense*)</u>: NOEC, shoot height and weight 10 mg/kg dry soil (nom.) EC_{50}, shoot weight **18 mg/kg dry soil (nom.)** <u>Rice (*Oryza sativa*)</u> NOEC, shoot height and weight 30 mg a.i./kg dry soil	*Thor GmbH:* <u>Oat (*Avena sativa*)</u>: NOEC, shoot weight 25.0 mg/kg dry soil (nom.) EC_{50}, shoot weight 44.2 mg/kg dry soil (nom.) <u>Oilseed rape (*Brassica napus)*</u> NOEC, shoot weight 12.5 mg/kg dry soil (nom.) EC_{50}, shoot weight 39.9 mg/kg dry soil (nom.) <u>*Pea (Pisum sativum)*</u> NOEC, shoot height and weight 100 mg/kg dry soil

(nom.) EC_{50}, shoot weight 80 mg a.i./kg dry soil (nom.)	(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			Remarks:
			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	
Preservation of water-based (emulsifiable and water soluble) metalworking fluids (MWF), PT 13	MIT containing biocidal products (KORDEK™ 573F, ACTICIDE® M 20 S)	Bacteria, Fungi	Aqueous concentrate	KORDEK™ 573F and ACTICIDE® M 20 S contain 50% and 20% MIT, respectively.	Dose directly into the use-dilution tanks of the MWF using a metering pump (semi-automated) to ensure correct dosage and uniformly dispersal throughout the system or dose fully automatically.	Dose as needed (typically single dose) to maintain control of the system.	1-6 weeks depending on the type of application and the results of the fluid monitoring	max 250 ppm	N/A	N/A	Limitations: Organizational and technical risk mitigation measures for high hazard chemicals must be applied during semi-automated introduction of biocidal products into MWF. Appropriate PPE must be worn during all phases of biocidal product use.

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 (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
A2/01	Petigara, R.B.	2001	Confidential attachment of Biocides product directives common core data set for active (chemical) substances, Parts 2 and 3: identity, and physical and chemical properties of Kordek® 573T Industrial Microbicide. Rohm and Haas Company, Report N° TR-01-059 (December 20, 2001), GLP, Unpublished.	Confidential	Rohm and Haas
A2/02	El A'mma, B.	2001	Product Chemistry Series 830 Group A: Product Identity, Composition and Analysis of ZONEN®-MT 100% As An Alternate to Kordek 573T Industrial Microbicide (EPA Registration No. 707-255). Rohm and Haas Company, CIS Research TR-01-032 (May 2001), Unpublished.	Confidential	Rohm and Haas
A2/03	[redacted]	2004	Method for Producing 2-Alkyl-4-Isothiazoline-3-one, [redacted]	Confidential	Rohm and Haas
A3/01	Betteley J.	2001	Kordek™ 573T Industrial microbicide physicochemical properties. Huntingdon Life Sciences Ltd., Huntingdon, UK. Technical Report N°: RAS 201/012606, 7 August 2001.	Y(ii)	Rohm and Haas
A3/02	Petigara R.B.	2000	Biocides Product Directives Common Core Data Set for Active (Chemical) Substances, Part 2 and 3: Identity, and physical and chemical properties of Kordek™ 573T Industrial microbicide. Rohm and Haas Company, Report N° TR-01-059 (December 20, 2001), Unpublished.	Y(ii)	Rohm and Haas
A3/03	Cihiy J.S.	1995	Product chemistry series 63: physical and chemical characterization studies of Kordek™ 573T Industrial Microbicide. Rohm and Haas Company, Research Laboratories, Spring House, USA. Technical Report N°: TR-95-31, August 31, 1995.	Y(ii)	Rohm and Haas
A3/04	Cihiy J.S.	1996	Product chemistry series 63: physical and chemical characterization studies of Kordek™ 573T Industrial Microbicide. Supplemental report to TR-95-31. Rohm and Haas Company, Research Laboratories, Spring House, USA. Technical Report N°: TR-96-13, 10 April 1996.	Y(ii)	Rohm and Haas
A4.1.a/01	Berrios, Efrain	2005	GLP validation of CIS test method N°. 01-71-03, Reverse phase HPLC analysis of RH-573, (Methylisothiazolone or MIT) in formulations and technical, for technical MIT, GLP-2005-021, October 20, 2005, Unpublished.	Y(ii)	Rohm and Haas
A4.1.a/02	Deepak, Doshi	2004	TM # 01-71-03, Reverse phase HPLC analysis for RH-573 (methylisothiazolone or MIT) in formulations and technical, February 4, 2004, Unpublished.	Y(ii)	Rohm and Haas
A4.1.a/03	Deepak, Doshi	2005	TM # 01-71-04, Reverse phase HPLC analysis for RH-573 (methylisothiazolone or MIT) in technical MIT samples, November 23, 2005, Unpublished.	Y(ii)	Rohm and Haas
A4.1.a/04	Eisenschmied, Mark A.	2005	GLP LC-MS peak identity verification of methylisothiazolone (MIT) in MIT technical as separated by CIS TM # 01-71-03, CAS Technical Document # TD2005-085, April 25, 2005, Unpublished.	Y(ii)	Rohm and Haas

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
A4.1.b/01	Berrios E.	2006	GLP validation and revision of APRAG analytical test method No. 94-144-01, analysis of RH-24,573 for organic impurities using reverse phase HPLC, Rohm and Haas Report # GLP-2005-032, January 17, 2006	Confiden-tial	Rohm and Haas
A4.1.b/02	Berrios E.	2006	CIS Test Method 05-97-01, "Analysis of Methylisothiazolone (MIT) for organic impurities using reverse phase HPLC",January 19, 2006.	Confiden-tial	Rohm and Haas
A4.1.b/03	Berrios E.	1994	APRAG test Method 94-144-01, "Analysis of RH-24,573 for organic impurities using reverse phase HPLC",October 10, 1994.	Confiden-tial	Rohm and Haas
A4.1.b/04	Eisenschmied, M.A.	2005	GLP LC-MS validation of APRAG TM # 94-144-01", CAS Technical Document # TD2005-136, July 12, 2005.	Confiden-tial	Rohm and Haas
A4.2.a/01	Marbo, M	2005	Validation of CIS analytic methods to determine RH-886 and RH-573 in soil and sediment Samples. Performed at Rohm and Haas Technical Center, Spring House, PA, USA, Technical Report N°. GLP-2005-009, December 12, 2005.	Y(ii)	Rohm and Haas
A4.2.b/01	Krainz Alexander	2006	Test method for the determination of 2-methyl-4-isothiazolin-3-one (RH-573) and 5-chloro-2-methyl-4-isothiazolin-3-one (RH-651) the active ingredients in RH-886 and RH-573 formulations, in air, Test method 857665, June 19, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.2.b/02	Krainz, Alexander	2006	Development and validation of residue analytical methods for determination of 2-methyl-4-isothiazolin-3-one (RH-573) and 5-chloro-2-methyl-4-isothiazolin-3-one (RH-651) the active ingredients in RH-886 and RH-573 formulations, in air, RCC Ltd., Study # 857665, Rohm and Haas Study # GLP-2005-012, June19, 2006, Unpublished.	Y(ii)	Rohm and Haas
A4.2.c/01	Krainz, Alexander	2007	Test method for the determination of 2-methyl-4-isothiazolin-3-one (RH-573) in drinking, surface and sea water, RCC Test Method A41084, March 13, 2007, Unpublished.	Y(ii)	Rohm and Haas
A4.2.c/02	Krainz, Alexander	2007	Development and validation of residue analytical methods for the determination of 2-methyl-4-isothiazolin-3-one (RH-573) in drinking, surface and sea water, RCC Ltd., Study # A41084, Rohm and Haas Report # GLP-2007-019, March 13, 2007, Unpublished.	Y(ii)	Rohm and Haas
A4.3/01	Krainz, Alexander	2007	Validation of a residue analytical method for the determination of 2-methyl-4-isothiazolin-3-one (RH-573) in acidic water, water containing ethanol and olive oil (food simulants), RCC Ltd., Study B05602, Rohm and Haas GLP-2007-048, May 31, 2007, Unpublished.	Y(ii)	Rohm and Haas
A4.3/02	Krainz, Alexander	2007	Test method for the determination of 2-methyl-4-isothiazolin-3-one (RH-573) in acidic water, water containing ethanol and olive oil (food simulants), RCC Ltd., Study B05602, Rohm and Haas, June 22, 2007, Unpublished.	Y(ii)	Rohm and Haas
A5.3.1/01	Diehl M A	2005	The Antimicrobial Activity of	Y(ii)[3]	Rohm

Annex I/IA (data generated/submitted after the entry into force of the Directive).

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

Section No / Reference No	**Author(s)**	**Year**	**Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published**	**Data Protection Claimed (Y/N)**	**Owner**
			Methylisothiazolinone (MIT): "Minimum Inhibitory Concentration (MIC) Studies versus Fungi, and Bacteria." Rohm and Haas Company, Technical Report Nº TR-05-039 (July 14, 2005), unpublished.		and Haas
A5.3.1/02	Diehl M A	2006	Speed of kill (SOK) and multiple challenge efficacy test with Methylisothiazolone (MIT) in an in-can model preservative system. Rohm and Haas Company, Technical Report Nº TR-06-018 (May 23, 2006), Unpublished.	Y(ii)	Rohm and Haas
A5.4.1/01	Williams T.M	2006	The Antimicrobial Mechanism of Action of Methylisothiazolinone (MIT). Rohm and Haas Company, Technical Report Nº TR-06-068 (August 28, 2006), unpublished.	Y(ii)	Rohm and Haas
A6.1.1/01	[redacted]	1999a	RH-573 Technical: acute oral toxicity study in male and female rats, Rohm and Haas Company Report N° 98R-212, April 7, 1999, Unpublished.	Y(ii)[4]	Rohm and Haas
A6.1.1/02	[redacted]	2002	Single dose oral toxicity/LD_{50} in rats with 2-methyl-4-isothiazolin-3-one, MB Research Laboratories Project N° MB 01-9694.01, Rohm and Haas Report N° 01RC-291, January 15, 2002, Unpublished.	Y(ii)	Rohm and Haas
A6.1.1/03	[redacted]	2000	Kordek™ 573T: Acute oral toxicity study in male and female mice, Rohm and Haas Co. Report N° 99R-131, January 31, 2000.	Y(ii)	Rohm and Haas
A6.1.1/04	[redacted]	(2006)	N-Methyl-malonamic acid acute oral toxicity study in male and female rats, Rohm and Haas Company Report N° 72R-1039 (November 13, 1972 original report; April 13, 2006 additional data), Unpublished.	Y(ii)	Rohm and Haas
A6.1.2/01	[redacted]	1999b	Kordek™ 573T: acute dermal toxicity study in male and female rats, Rohm and Haas Company, Rohm and Haas Report N° 99R-061A, October 15, 1999.	Y(i)	Rohm and Haas
A6.1.3.a/01	[redacted]	1995	RH-573 Technical: acute inhalation toxicity study in rats. Rohm and Haas Company Report N° 95R-113, September 26, 1995.	Y(i)	Rohm and Haas
A6.1.3.a/02	[redacted]	2001	Kordek™ 573F: acute inhalation toxicity study in rats, Rohm and Haas Company, Rohm and Haas Report N° 01R-100 (July 23, 2001), Unpublished.	Y(ii)	Rohm and Haas
A6.1.3.a/03	[redacted]	2002	Kordek™ 573F: acute inhalation toxicity study in rats, Supplemental Report, Rohm and Haas Company, Rohm and Haas Report N° 01R-100A (January 16, 2002), Unpublished.	Y(ii)	Rohm and Haas
A6.1.3.b/01	[redacted]	1994	RH-573 upper airway irritation RD_{50} evaluation in mice, International Research and Development Corporation Project ID: 285-055, Rohm and Haas Report N° 94RC-176, December 20, 1994.	Y(i)	Rohm and Haas
A6.1.4/01	[redacted]	1997	RH-573 Technical: skin irritation study in rabbits,	Y(i)[5]	Rohm

to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA (data generated/submitted after the entry into force of the Directive).[3] Y(ii) : Data protection claimed in accordance with Article 12.1(c) (ii) : Active substance already on the market on 14 May 2000, data submitted for the first time in support of the first inclusion in Annex I or IA.

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

Section No / Reference No	**Author(s)**	**Year**	**Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published**	**Data Protection Claimed (Y/N)**	**Owner**
			Rohm and Haas Company, Rohm and Haas Company Report N° 96R-123, January 23, 1997.		and Haas
A6.1.4/02	[redacted]	2005	2-Methyl-4-isothiazolin-3-one - corrosivity in vitro skin corrosion assay using EPI-DERM (EPI-200): 3 and 60 minute exposure protocol, Institute for In-Vitro Sciences Study N° 04AF50.050079, Rohm and Haas Report No° 04RC-058 (April 6, 2005), Unpublished.	Y(ii)[6]	Rohm and Haas
A6.1.5/01	[redacted]	1989	RH-24,573: Delayed contact hypersensitivity study in guinea pigs, Rohm and Haas Company Report N° 88R-052, April 28, 1989.	Y(i)	Rohm and Haas
A6.1.5/02	[redacted]	2000	Methylisothiazolinone: Dermal sensitization study in guinea pigs Maximization test, Rohm and Haas Company Report N° 00R-187, December 19, 2000.	Y(ii)	Rohm and Haas
A6.1.5/03	[redacted]	2001	Methylisothiazolinone 20 % - Open epicutaneous test in guinea pigs, BASF Laboratories Project ID: 31H0366/002119, US Ref N° 01RC-1031, July 12, 2001.	Y(ii)	Rohm and Haas
A6.1.5/04	[redacted]	2003a	Methylisothiazolone: Local lymph node assay, Calvert Laboratories Report N° 0787XR07.002, Rohm and Haas Report N° 02RC-063, August 8, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.1.5/05	[redacted]	2003b	N-(Methyl) malonamic acid: Local lymph node assay, Calvert Laboratories Report N°: 0787XR07.001, Rohm and Haas Report No: 02RC-049 (August 8, 2003), Unpublished.	Y(ii)	Rohm and Haas
A6.12.3/01	Nave V.A.	2006	Worker health incidents resulting from exposure to 2-Methyl-4-isothiazolin-3-one (RH-573); Rohm and Haas Company, Memo N° 06M-027 (May 10, 2006), Unpublished.	Y(ii)	Rohm and Haas
A6.12.6/01	Wucinich R., Aust L., and Yarbrough G.K.	1994	RH-573 Evaluation of 21-day cumulative irritation potential in humans. Hill Top Research, Inc., Hill Top Research Report N° 92-3368-73, Rohm and Haas Report N° 92RC-097A (March 28, 1994), Unpublished.	Y(ii)	Rohm and Haas
A6.12.6/02	Shelanski, M.V.	2000	A patch test procedure to determine the skin irritation and sensitization propensities of Kordek™ 50C. Product Investigations PII N° 11801, Rohm and Haas Report N° 99RC-138 (February 15, 2000), Unpublished.	Y(ii)[7]	Rohm and Haas
A6.12.6/03	Georgeian K.	2000a	Repeated insult patch study with 2-methylisothiazolin-3-one at an aqueous concentration of 200 ppm active ingredient. TKL Research Study N° DS103400, Rohm and Haas Report N° 00RC-0099A, July 26, 2000.	Y(ii)	Rohm and Haas
A6.12.6/04	Georgeian K.	2000b	Repeated insult patch study with 2-methylisothiazolin-3-one at an aqueous concentration of 300 ppm active ingredient. TKL Research Study N° DS105500, Rohm and Haas	Y(ii)	Rohm and Haas

[5] Y(i) : Data protection claimed in accordance with Article 12.1(c) (i) : Active substance already on the market on 14 May 2000. Information submitted for the purposes of the Directive. Information already submitted to the MS before 14 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA (data already submitted before the entry into force of the Directive).

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

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

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			Report N° 00RC-0099B, September 22, 2000.		
A6.12.6/05	Georgeian, K.	2001a	Repeated insult patch study with methylisothiazolone at an aqueous concentration of 400 ppm active ingredient. TKL Research Study N° DS105000/107500, Rohm and Haas Report N° 00RC-0099D (February 26, 2001), Unpublished.	Y(ii)	Rohm and Haas
A6.12.6/06	Georgeian, K.	2001b	Repeated insult patch study with methylisothiazolone at an aqueous concentration of 500 ppm active ingredient. TKL Research Study N° DS107800/109000/100801 and DS103601, Rohm and Haas Report N° 00RC-0099E (June 14, 2001) and 00RC-0099F (November 14, 2001), Unpublished.	Y(ii)	Rohm and Haas
A6.12.6/07	Georgeian, K. and Vendetti, N.	2002	Repeated insult patch study with methylisothiazolone at an aqueous concentration of 600 ppm active ingredient. TKL Research Study N° DS103701/105301/106601/ 107401 and DS101802/103402, Rohm and Haas Report N° 00RC-0099G and 00RC-0099H (September 4, 2002), Unpublished.	Y(ii)	Rohm and Haas
A6.15/01	Quérou, R. and Lévy, R.	2007	Calculation of the maximum loading of MIT in food contact packaging materials in a worst case situation. Rohm and Haas company report N°0705_RQ, March 15, 2007, Unpublished.	Y(ii)	Rohm and Haas
A6.2/01	Hazelton G.A.	2003	In vitro percutaneous absorption through rat skin, Rohm and Haas Company, Rohm and Haas Company Report N° 00R-066, August 22, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.2/02	[redacted]	2005	2-Methyl-4-isothiazolin-3-one (MIT): in vitro absorption from water and three formulations through human epidermis, Central Toxicology Laboratory Study No: JV1839, Rohm and Haas Report N° 04RC-066 (August 16, 2005), Unpublished.	Y(ii)	Rohm and Haas
A6.2/03	[redacted]	2003.	Tissue distribution of ^{14}C-RH-573 in the mouse. XenoBiotic Laboratories, Inc., unpublished report, XBL Study N° XBL03171, Rohm and Haas Company Report N° 03RC-042, August 27, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.2/04	[redacted]	2005a	Metabolism and pharmacokinetics of ^{14}C-RH-573 in the rat, XenoBiotic Laboratories Report N° XBL01057, Rohm and Haas Report N° 03RC-043, June 13, 2005, Unpublished.	Y(ii)	Rohm and Haas
A6.2/05	[redacted]	2005b	Metabolism of 14C-RH-573 in the biliary cannulated rat, XenoBiotic Laboratories Report No. RPT01215, Rohm and Haas Report N° 04RC-056 (July 14, 2005), Unpublished.	Y(ii)	Rohm and Haas
A6.3.1/01	[redacted]	1984	Kathon™ 886 MW: one month oral toxicity study in rabbits, Rohm and Haas Company, Rohm and Haas Report N° 84R-095, August 31, 1984.	Y(i)	Rohm and Haas
A6.4.1.a/01	[redacted]	2000	RH-573 Technical: three month drinking water toxicity study in rats, Rohm and Haas Company, Rohm and Haas Report N° 99R-135, April 7, 2000, Unpublished.	Y(ii)	Rohm and Haas
A6.4.1.a/02	[redacted]	1975	RH-886T, RH-35,375 and RH-00,345: three month subchronic oral safety evaluation study in rats (metabolite). International Research and Development Corporation Study No: 285-010, Rohm and Haas Report No: 75RC-1001 (February 17, 1975), Unpublished.	Y(ii)	Rohm and Haas
A6.4.1.b/01	[redacted]	2004	2-Methyl-4-isothiazolin-3-one: A 13-week dietary toxicity study in dogs, MPI Research, Inc., Mattawan, MI, USA, MPI Study N° 285-069,	Y(ii)	Rohm and Haas

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			Rohm and Haas Company Report N° 03RC-030, February 26, 2004, Unpublished.		
A6.4.1.b/02	[redacted]	1975	RH-886T, RH-35,375 and RH-00,345: three month subchronic oral safety evaluation study in Beagle dogs (metabolite). International Research and Development Corporation Study No: 285-008, Rohm and Haas Report No: 75RC-1002 (February 19, 1975), Unpublished.	Y(ii)[8]	Rohm and Haas
A6.4.2/01	[redacted]	1982	Kathon™ 886 MW: 90-day percutaneous toxicity study in rabbits. Rohm and Haas Company, Rohm and Haas Report N° 80R-119, August 31, 1982, Unpublished.	Y(i)	Rohm and Haas
A6.4.3/01	[redacted]	1984	Kathon™ 886 MMPA Process: thirteen-week inhalation toxicity study in rats, Rohm and Haas Company, Rohm and Haas Report N° 82R-245, December 10, 1984, Unpublished.	Y(i)	Rohm and Haas
A6.5.1/01	[redacted]	1994	Kathon™ biocide: 24-month drinking water chronic/oncogenic study in rats, Rohm and Haas Company, Rohm and Haas Report N° 90R-149, January 24, 1994, Unpublished.	Y(ii)	Rohm and Haas
A6.5.2/01	[redacted]	1983	Kathon™ CG: 30-month dermal carcinogenesis study in male mice, Rohm and Haas Company, Rohm and Haas Report N° 81R-288, January 14, 1983, Unpublished.	Y(ii)	Rohm and Haas
A6.6.1/01	Sames, J.L. and Streelman D.R.	1999	Kordek™ 573T: Salmonella typhimurium gene mutation assay, Rohm and Haas Company, Rohm and Haas Report N° 99R-062, July 19, 1999.	Y(ii)	Rohm and Haas
A6.6.1/03 (non key)	Melly, J.G. and Lohse K.L.	1982	2-Methyl-4-isothiazolin-3-one: microbial mutagen test, Rohm and Haas Company, Rohm and Haas Report N° 81R-301, February 3, 1982.	Y(i)[9]	Rohm and Haas
A6.6.2/01	[redacted]	2000	Mutagenicity test on Kordek™ 573T: measuring chromosomal aberrations in Chinese hamster ovary (CHO) cells, Covance Laboratories Study Number 20879-0-0437OECD, Rohm and Haas Report N° 99RC-133, February 2, 2000.	Y(i)[10]	Rohm and Haas
A6.6.2/02 (non key)	Hilliard C.A., Armstrong M.J., Bradt C.I., Hill R.B., Greenwood S.K., and Galloway S.M.	1998	Chromosome aberrations in vitro related to cytotoxicity of non mutagenic chemicals and metabolic poisons. Environmental and Molecular Mutagenesis 31:316-326.	-	-
A6.6.3/01:	[redacted]	2000	Kordek™ 573T: Test for chemical induction of	Y(ii)[11]	Rohm

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

[9] Y(i) : Data protection claimed in accordance with Article 12.1(c) (i) : Active substance already on the market on 14 May 2000. Information submitted for the purposes of the Directive. Information already submitted to the MS before 14 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA (data already submitted before the entry into force of the Directive).

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

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

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			gene mutation at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation with a confirmatory assay, Sitek Research Laboratories Study N° 0581-2510, Rohm and Haas Report N° 99RC-265, April 13, 2000, Unpublished.		and Haas
A6.6.4/01	[redacted]	2000	Kordek™ 573T: micronucleus assay in CD-1 mouse bone marrow cells, Rohm and Haas Company, Rohm and Haas Report N° 99R-132, March 30, 2000.	Y(i)	Rohm and Haas
A6.6.4/02	[redacted]	2003	2-Methyl-4-isothiazolin-3-one (RH-573): In Vivo/In Vitro unscheduled DNA synthesis in rat primary hepatocyte cultures at two timepoints with a dose rangefinding assay, Covance Laboratories Study N° 25074-0-494 OECD, Rohm and Haas Report N° 03RC-044, August 25, 2003.	Y(ii)	Rohm and Haas
A6.6.7/01	San, R.H.C. and VanDyke, M.R.	2005	N-Methyl Malonamic Acid: bacterial reverse mutation assay (metabolite), BioReliance Study N° AB13CE.503.BTL, Rohm and Haas Report N° 05RC-045 (September 9, 2005), Unpublished.	Y(i)	Rohm and Haas
A6.7.1/01	[redacted]	1994	Kathon™ biocide: 24-month drinking water chronic/oncogenic study in rats, Rohm and Haas Company, Rohm and Haas Report N° 90R-149, January 24, 1994, Unpublished.	Y(ii)	Rohm and Haas
A6.7.1/02	[redacted]	1983	Kathon™ CG: 30-month dermal carcinogenesis study in male mice, Rohm and Haas Company, Rohm and Haas Report N° 81R-288, January 14, 1983.	Y(i)[12]	Rohm and Haas
A6.8.1.a/01	[redacted]	2003b	An oral (gavage) developmental toxicity study of 2-methyl-4-isothiazolin-3-one in rats, WIL Research Labs Study N° WIL-91012, Rohm and Haas Report N° 02RC-122, September 30, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.8.1.b/01	[redacted]	2003a	An oral (gavage) developmental toxicity study of 2-methyl-4-isothiazolin-3-one in rabbits, WIL Research Labs Study N° WIL-91006, Rohm and Haas Report N° 01RC-269, September 16, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.8.2/01	[redacted]	2003c	A two-generation reproductive toxicity study of 2-methyl-4-isothiazolin-3-one administered via drinking water in rats, WIL Research Laboratories, Inc., Study N° WIL-91005, Rohm and Haas Report N° 01RC-285, October 1, 2003, Unpublished.	Y(ii)	Rohm and Haas
A6.8.2/02	[redacted]	2007	A two-generation reproductive toxicity study of 2-methyl-4-isothiazolin-3-one administered via drinking water in rats, Histopathology of the brain. Report N° 01RC-285A, March 2, 2007, Unpublished.	Y(ii)	Rohm and Haas
A6.9/01	Du, S. et al.	2002	*In vitro* neurotoxicity of methylisothiazolinone, a commonly used industrial and household biocide, proceeds via zinc and extracellular signal-regulated kinase mitogen-activated protein kinase-dependent pathway. *The Journal of neuroscience*, September 1, 2002, **22**(17):7408-7416, Published.	N	/
A6.9/02	He, K. et al.	2004	Lack of phosphorylation of tyrosine 576 of focal adhesion kinase correlates to neurite outgrowth deficiency following methylisothiazolinone	N	/

[12] Y(i) : Data protection claimed in accordance with Article 12.1(c) (i) : Active substance already on the market on 14 May 2000. Information submitted for the purposes of the Directive. Information already submitted to the MS before 14 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA (data already submitted before the entry into force of the Directive).

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			treatment in cultured cortical neurons. Poster board number B266.		
A6.9/03	[redacted]	1984	A dermal carcinogenesis study in male mice with Kathon™ CG. Poster board number 145.	N	/
A7.1.1.1.1/01	Marx, M, Castle, S, and Shepler, K.	1992	Hydrolysis of ^{14}C RH-573 at pH 5, 7, and 9; Pharmacology and Toxicology Research Laboratory-West, Richmond, CA USA, PTRL Report N° 223W-1 Rohm and Haas Company, Technical Report N° 34-92-63 (6 November 1992), unpublished.	**Y(i)**[13]	Rohm and Haas
A7.1.1.1.2/01	Shepler, K..	1995	Sunlight Photodegradation of ^{14}C RH-573 (the Minor Component of RH-886) in a Buffered Aqueous Solution at pH 7; PTRL West, Inc. Richmond, CA, USA, PTRL Project N° 224W, Rohm and Haas Technical Report N° 34-94-78 (May 4, 1995), Unpublished.	**Y(i)**	Rohm and Haas
A7.1.1.2.1/01	Bashir, M.	1998	Ready Biodegradation of ^{14}C-RH-573: Modified Sturm Test, Covance Laboratories, Inc., Madison, WI, USA, Covance Study N° 6228-141, Rohm and Haas Biocide Technical Report N° TR97-076 (March 26, 1998), Unpublished.	**Y(i)**	Rohm and Haas
A7.1.2.1.1/01	Oteyza, T., Gillings, E. and Roberts, G.C.	2007	RH-573: Simulation test for aerobic sewage treatment by activated sludge. Brixham Environmental Laboratories, Brixham, Devon, UK. Brixham Report N°. BL8162/B, Rohm and Haas Technical Report N° TR-07-012, Unpublished.	Y(ii)	Rohm and Haas
A7.1.2.2.1.a/01	Guo I., Marbo M., Jacobson A.	2007	Aerobic Transformation of RH-573 in Surface Water, Rohm and Haas company, Rohm and Haas report N°GLP-2007-041, August 10, 2007, Unpublished.	**Y(ii)**	Rohm and Haas
A7.1.2.2.2.a/01	Reynolds J. L.	1994	Aerobic Aquatic Metabolism of ^{14}C RH-573; XenoBiotic Laboratories, Inc. Plainsboro, NJ, USA. XenoBiotic Report N° RPT 00170, Rohm and Haas Technical Report N° 34-94-122 (30 September 1994), Unpublished.	**Y(i)**	Rohm and Haas
A7.1.2.2.2.a/02	Schuck, H.	2002	Aerobic Transformation of RH-573 in Aquatic Sediment Systems, Rohm and Haas Research Laboratories, Spring House, PA, USA, Rohm and Haas Technical Report N° TR-02-010 (July 31, 2002), Unpublished.	Y(ii)	Rohm and Haas
A7.1.2.3/01	Seyfried B.	2003	Ready Biodegradation of N-methyl Malonamic Acid in a CO_2 Evolution (Modified Sturm) Test; RCC Ltd, CH-4452 Itingen, Switzerland, RCC Study N°.: 843966, Rohm and Haas Report N° GLP-2002-081 (April 22, 2003), Unpublished.	**Y(ii)**	Rohm and Haas
A7.1.2.3/02	Seyfried B.	2003	Ready Biodegradation of N-methyl Acetamide in a CO2 Evolution (Modified Sturm) Test; RCC Ltd, CH-4452 Itingen, Switzerland, RCC Study No.: 843967, Rohm and Haas Report N° GLP-2003-031 (November 5, 2003), Unpublished.	**Y(ii)**	Rohm and Haas
A7.1.2.3/03	Seyfried B.	2003	Ready Biodegradation of Malonamic Acid in a CO_2 Evolution (Modified Sturm) Test; RCC Ltd, CH-4452 Itingen, Switzerland, RCC Study No.: 843968, Rohm and Haas Report N° GLP-2003-032 (November 5, 2003), Unpublished.	**Y(ii)**	Rohm and Haas
A7.1.3/01	Swales S.	2002	14C-RH-573: Activated Sludge Adsorption Isotherm; Covance Laboratories Ltd., North	Y(ii)	Rohm and

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

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			Yorkshire England, Covance Report No. 616/31-D2149, Rohm and Haas Report N° 02RC-0031 (December 23, 2002), Unpublished.		Haas
A7.1.3/02 (non key)	Reynolds J.L.	2001	Reynolds J.L., 2001, Adsorption and Desorption of ^{14}C RH-573 in Three Soils and One Sediment; XenoBiotic Laboratories, Inc., Plainsboro, New Jersey, USA, XBL Report N° RPT00653, Rohm and Haas Company Technical Report N° 00-033.	Y(ii)	Rohm and Haas
A7.1.3/03	Gillings, E.	2006	RH-573: Adsorption and Desorption to Soil; Brixham Environmental Laboratories, Brixham, Devon, UK. Brixham Report N°. BL8308/B, Rohm and Haas Technical Report N° 06-058 (29 August 2006), Unpublished.	Y(ii)	Rohm and Haas
A7.2.1/01	Guo, I	2006	Aerobic Transformation of RH-573 in Soil. Performed at Rohm and Haas Technical Center, Spring House, PA, USA, Technical Report N°. GLP-2006-012, (December 12, 2006), Unpublished.	Y(ii)	Rohm and Haas
A7.2.3.1/01	Reynolds J.L.	1996	Age leaching of ^{14}C-RH-651 in four soils, Xenobiotic Laboratories, Inc., Report N°RPT00171, Rohm and Haas Company, Rohm and Haas Report N°34-95-91, July 18, 1996, Unpublished.	Y(ii)	Rohm and Haas
A7.3.1/01	Guo, I.	2003	Calculation of Tropospheric Phototransformation of Isothiazolone Compounds; Rohm and Haas Company, Rohm and Haas Technical Report N° TR-03-001 (May 15, 2003), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.1.a /01:	[redacted]	2001	2-Methyl-4-isothiazolin-3-one, technical: Flow-through acute toxicity to the Rainbow Trout, *Oncorhynchus mykiss*, TR Wilbury Laboratories Study N° 2125-RH, Rohm and Haas Report N° 00RC-0248, October 2, 2001, Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.1.a /02 (non key)	[redacted]	1983	Acute toxicity of RH-573 to bluegill *(Lepomis macrochirus)*, EG&G Bionomics Report N° BW-83-4-1384, Rohm and Haas Report N° 83RC-37, April 1983.	Y(ii)	Rohm and Haas
A7.4.1.1.a /03 (non key)	[redacted]	1983	Acute toxicity of RH-573 to rainbow trout *(Salmo gairdneri)*, EG&G Bionomics Report N° BW-83-4-1385, Rohm and Haas Report N° 83RC-38, April 1983.	Y(ii)	Rohm and Haas
A7.4.1.1.b /01	[redacted]	**2004**	2-Methyl-4-isothiazolin-3-one: Acute toxicity with the sheepshead minnow, *Cyprinodon variegatus*, determined under flow-through conditions. ABC Laboratories Study N°: 48827, Rohm and Haas Report N° 04RC-016 (July 22, 2004), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.1.c /01	[redacted]	2002	Acute toxicity of N-methyl malonamic acid to the rainbow trout, Oncorhynchus mykiss, determined under static test conditions (metabolite), ABC Laboratories Project ID 47178, Rohm and Haas Report No 01RC-300 (September 30, 2002), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.1.c /02	[redacted]	2002	Acute toxicity of N-methyl acetamide to the rainbow trout, Oncorhynchus mykiss, determined under static test conditions (metabolite), ABC Laboratories Study No 47185, Rohm and Haas Report No 01RC-303 (August 5, 2002), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.1.c /03	[redacted]	2002	Acute toxicity of malonamic acid to the rainbow trout, Oncorhynchus mykiss, determined under static test conditions. (metabolite), ABC Laboratories Study No 47182, Rohm and Haas Report No 01RC-306 (September 13, 2002), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.2.a	[redacted]	**2001**	2-Methyl-4-isothiazolin-3-one technical: flow-	Y(ii)	Rohm

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
/01	[redacted]		through acute toxicity to the Daphnid, *Daphnia magna*, TR Wilbury Laboratories Study N° 2124-RH, Rohm and Haas Report N° 00RC-249 (August 1, 2001), Unpublished.		and Haas
A7.4.1.2.a /02 (non key)	Surprenant DC	1983	Acute toxicity of RH-573 to *Daphnia magna*, EG&G Bionomics Report N° BW-83-3-1388, Rohm and Haas Report N° 83RC-39, March 1983.	Y(ii)	Rohm and Haas
A7.4.1.2.b /01	Hughes, C.	**2004**	2-Methyl-4-isothiazolin-3-one: acute toxicity with the mysid shrimp, *Americamysis bahia*, determined under flow-through conditions, ABC Laboratories Study N° 48828, Rohm and Haas Report N° 04RC-017 (August 16, 2004), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.2.c /01	Madsen T.	**2002**	Acute toxicity of N-methyl malonamic acid to the water flea, *Daphnia magna*, determined under static test conditions (metabolite), ABC Laboratories Study N° 47177, Rohm and Haas Report N° 01RC-301 (August 13, 2002), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.2.c /02	Rhodes J.E.	**2002**	Acute toxicity of N-methyl acetamide to the water flea, *Daphnia magna*, determined under static test conditions. (metabolite), ABC Laboratories Study N° 47184, Rohm and Haas Report N° 01RC-304 (August 5, 2002), Unpublished.	Y(ii)	Rohm and Haas
A7.4.1.2.c /03	Madsen T.	2002	Acute toxicity of malonamic acid to the water flea, *Daphnia magna,* determined under static test conditions (metabolite), ABC Laboratories Study N° 47181, Rohm and Haas Report N° 01RC-307 (September 10, 2002), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.1.3.a /01	Ward TJ, Magazu JP, and Boeri RL	**1997**	Toxicity of RH-573 technical to the freshwater alga, Selenastrum capricornutum, TR Wilbury Laboratories Study N° 1036-RH, Rohm and Haas Report N° 95RC-164, March 25, 1997, Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.1.3.b /01	Hughes C	2004	2-Methyl-4-isothiazolin-3-one: toxicity with the marine diatom, *Skeletonema costatum*, determined under static conditions, ABC Laboratories Study N° 48829, Rohm and Haas Report N° 04RC-0018 (October 22, 2004), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.1.3.c /01	Madsen T.	**2002**	Toxicity of N-methyl malonamic acid to the unicellular green alga, *Selenastrum capricornutum*, (metabolite), ABC Laboratories Study N° 47179, Rohm and Haas Report N° 01RC-302 (September 9, 2002), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.1.3.c /02	Rhodes J.E.	**2002**	Toxicity of N-methyl acetamide to the unicellular green alga, *Selenastrum capricornutum*, (metabolite), ABC Laboratories Study N° 47186, Rohm and Haas Report N° 01RC-305 (September 5, 2002), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.1.3.c /03	Madsen T.	2002	Toxicity of malonamic acid to the unicellular green alga, *Selenastrum capricornutum*, (metabolite), ABC Laboratories Study N° 47183, Rohm and Haas Report N° 01RC-308 (September 20, 2002), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.1.4/01	Ward, T.J., Magazu, J.P., and Boeri, R.L.	1996	Activated sludge respiration inhibition test with RH-573 technical, TR Wilbury Study N° 1037-RH, Rohm and Haas Report N° 95RC-0165 (September 26, 1996), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.3.2/01	[redacted]	2005	Early life-stage toxicity of 2-methyl-4-isothiazolin-3-one to the rainbow trout, Oncorhynchus mykiss, under flow-through	**Y(ii)**[14]	Rohm and Haas

[14] Data on existing a.s. submitted for the first time in support of the first inclusion into annex I/IA. Data protection claimed in accordance with the Article 12.1 (c) (ii).

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			conditions. ABC Laboratories Study No: 48835. Rohm and Haas Report N° 04RC-023 (March 11, 2005), Unpublished.		
A7.4.3.3.1/01 (non key)	Jacobson, A.	1995	RH-573 Fish Bioaccumulation: Calculation of Whole Fish Bioconcentration Factor From Research Report N° 23-48 (1972), Rohm and Haas Company Technical Report No. 34-95-26.	Y(ii)	Rohm and Haas
A7.4.3.4/01	Hicks SL	2004	2-Methyl-4-isothiazolin-3-one: Chronic toxicity test with the water flea, *Daphnia magna*, conducted under flow-through conditions. ABC Laboratories Study N° 48836, Rohm and Haas Report N° 04RC-0024, November 8, 2004, Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.3.5.1.a/01	Aufderheide J.	2006	2-methyl-4-isothiazolin-3-one: Chronic toxicity in whole sediment to freshwater midge *Chironomus riparius.* ABC Laboratories Study N° 49009, Rohm and Haas Report N° 04RC-055 (January 25, 2006), Unpublished.	**Y(ii)**	Rohm and Haas
A7.4.3.5.1.a/02	Thomas S.T., Krueger, H.O., Kendall, T.Z. and Nixon, W.B.	2007	2-methyl-4-isothiazolin-3-one: A sediment-water *Lumbriculus* toxicity test using spiked sediment, Wildlife International Ltd Project No 129A-131, Rohm and Haas report No 06RC-227 (July 19, 2007), Unpublished	**Y(ii)**	Rohm and Haas
A7.4.3.5.1.a/03	Thomas S.T., Krueger, H.O., Kendall, T.Z. and Nixon, W.B.	2008	2-methyl-4-isothiazolin-3-one: A prolonged sediment toxicity test with *Hyalella azteca* using spiked sediment, Wildlife International Ltd Project No 129A-131, Rohm and Haas report No 06RC-227 (July 19, 2007), Unpublished	**Y(ii)**	Rohm and Haas
A7.5.1.1/01	Serak K.	2005a	Determination of the effect of 2-methyl-4-isothiazolin-3-one on the carbon transformation activity of soil microorganisms. ABC Laboratories Study N° 48831, Rohm and Haas Report N° 04RC-025 (May 6, 2005), Unpublished.	**Y(ii)**	Rohm and Haas
A7.5.1.1/02	Serak K.	2005b	Determination of the effect of 2-methyl-4-isothiazolin-3-one on the nitrogen transformation activity of soil microorganisms. ABC Laboratories Study N° 48830, Rohm and Haas Report N° 04RC-019 (October 19, 2005), Unpublished.	Y(ii)	Rohm and Haas
A7.5.1.1.a/03	Tunink, A.	2009	Determination of the effect of 2-methyl-4-isothiazolin-3-one on the nitrogen transformation of soil microorganisms. ABC Laboratories Study No 64255, Rohm and Haas Report No 08RC-144 (January 26, 2009), Unpublished	Y(ii)	Rohm and Haas
A7.5.1.2/01	Warbritton R	2004	Acute toxicity of 2-methyl-4-isothiazolin-3-one to the earthworm, Eisenia fetida, ABC Laboratories Study N° 48832, Rohm and Haas Report N°: 04RC-020, October 1, 2004, Unpublished.	Y(ii)	Rohm and Haas
A7.5.1.3/01	Aufderheide J	2005	Effects of 2-methyl-4-isothiazolin-3-one on the seedling emergence and early seedling growth of selected non-target terrestrial plants, ABC Laboratories 48833, Rohm and Haas Report N° 04RC-021, January 3, 2005, Unpublished.	Y(ii)	Rohm and Haas
A7.5.3.1.1/01	[redacted]	1990a	Kathon® 886 biocide: 21-day acute oral LD_{50} study in bobwhite quail. Bio-Life Associates Project ID: BLAL 90 QD 148. Rohm and Haas Report N°: 89RC-0339 (August 14, 1990), Unpublished.	Y(i)	Rohm and Haas
A7.5.3.1.1/02 (non key)	[redacted]	1976	Acute oral LD_{50} – bobwhite quail Kathon 886, Wildlife International Project N° 129-114; Rohm and Haas Report N° 76RC-1125 (November 2, 1976), Unpublished.	Y(i)	Rohm and Haas
A7.5.3.1.2/01	[redacted]	1990b	Kathon® 886 biocide: 8-day acute dietary LC_{50} study in mallard ducklings. Bio-Life Associates Project ID: BLAL 90 DC 145. Rohm and Haas	Y(i)	Rohm and Haas

Section No / Reference No	Author(s)	Year	Title. Source (if different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Y/N)	Owner
			Report N° 89RC-0341 (October 18, 1990), Unpublished.		
A7.5.3.1.2 /02	[redacted]	1990c	Kathon® 886 biocide: 8-day acute dietary LC50 study in bobwhite quail. Bio-Life Associates Project ID: BLAL 90 QC 148. Rohm and Haas Report ° 89RC-0340 (October 18, 1990), Unpublished.	Y(i)	Rohm and Haas
A7.5.3.1.2 /03 (non key)	[redacted]	1972	Subacute toxicity studies with RH-886-T in bobwhite quail and pekin ducks. Affiliated Medical Research, Inc. Contract No: 120-1587-72. Rohm and Haas Report N° 72RC-1010 (September 7, 1972), Unpublished.	Y(i)	Rohm and Haas
B6.2a/02	[redacted]	1999a	Kordek™ 50C: Acute oral toxicity study in male and female rats, Rohm and Haas Company, Rohm and Haas Report N° 99R-057 (September 2, 1999) Unpublished.	Y(ii)[15]	Rohm and Haas
B5.10/01	Diehl, M.A.	2006	The Antimicrobial Activity of Methylisothiazolinone (MIT): Frame Formulation Minimum Inhibitory Concentration (MIC) Studies versus Bacteria and Fungi; TR-06-002; Not GLP, Unpublished.	Y(ii)[16]	Rohm and Haas
B5.10/02	Williams T.W. and Diehl M.A.	2006	Technical Report on the Antimicrobial Efficacy of Methylisothiazolinone (MIT) Biocidal Products for Product Type 13: Metalworking Fluid Preservatives; BPD-06-015; Not GLP, Unpublished.	Y(ii)	Rohm and Haas

Section No / Reference No[17]	Author(s) [18]	Year	Title[19] 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]	Y	Thor GmbH

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

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

[17] ***Section Number/Reference Number*** should refer to the section number in Doc III-A or III-B. If the study is non-key, and hence not summarised in Doc III but mentioned in Doc II, it should be included in the reference list alongside related references and its location in Doc II indicated in brackets. (If there is a need to include a cross-reference to PPP references then an additional column can be inserted).

[18] ***Author's Name*** should include the author's surname before initial (s) to enable the column to be sorted alphabetically. If the Human Rights Charter prevents author's surnames on unpublished references being included in non-confidential documents, then it will be necessary to consider including 'Unpublished [number/year & letter] ' in Doc II, and both ' Unpublished [number/year & letter]' and the 'Authors Name' in the reference list'. This may necessitate the need for an additional column to state whether a reference is unpublished which can then be sorted.

[19] ***Title, Source (where different from company), Company, Report No., GLP (where relevant), (Un)Published*** should contain information relevant to each item (ideally on separate lines within the table cell for clarity). If useful, the name of the electronic file containing the specific study/reference could be added in brackets.

Section No / Reference No[17]	Author(s) [18]	Year	Title[19] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			[redacted] GLP, Unpublished		
III-A 2	Thor	2007	Sales Specification Acticide M 50; Thor GmbH; Unpublished	Y	Thor GmbH
III-A 2 **III-B 2**	Thor	2007	Sales Specification Acticide M 20 S; Thor GmbH; Unpublished	Y	Thor GmbH
III-A 2 **III-B 2**	Thor	2007	Sales Specification Acticide M 10 S; Thor GmbH; Unpublished	Y	Thor GmbH
III-A 3.3	Brauch G	2007	SDB ACTICIDE MIT&A 1021&GB.pdf Thor GmbH; Published	N	Thor GmbH
III-A 3.1.1	[redacted]	1999	Determination of the Melting Point of 2-Methyl-4-isothiazoline-3-one (MIT) according to OECD Guideline No. 102; [redacted]; GLP; Unpublished	Y	Thor GmbH
III-A 3.1.2 **III-A 3.10**	[redacted]	2002	Determination of the Boilung Point/Boiling Range of 2-Methyl-3(2H)-isothiazolone; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.1.3	[redacted]	2002	Determination of the Density of 2-Methyl-3(2H)-isothiazolone; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.2	[redacted]	2000	2-Methyl-4-isothiazoline-3-one (MIT) - Vapour Pressure; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.2	[redacted]	2006	Determination of the vapour presure of 2-Methyl-2H-isothiazol-3-one (MIT); [redacted]; GLP; Unpublished	Y	Thor GmbH
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;	Y	Thor GmbH

Section No / Reference No[17]	Author(s) [18]	Year	Title[19] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			[redacted] Non- GLP; Unpublished		
III-A 3.5-01	[redacted]	1999	Determination of the Water Solubility of 2-Methyl-4-isothiazoline-3-one (MIT) following OECD Guideline No. 105; [redacted]; GLP; Unpublished	Y	Thor GmbH
III-A 3.5-02	[redacted]	2002	Determination of the Water Solubility of 2-Methyl-3(2H)-isothiazolone Including Effect of pH and Temperature; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.6	[redacted]	1996	Dissociation Constant in Water in analogy to OECD-Guideline No. 112 2-Methyl-4-isothiazoline-3-one (MIT) following OECD Guideline No. 105; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 3.7	[redacted]	1996	Solubility in n-Heptane and Xylene 2-Methyl-4-isothiazoline-3-one (MIT); [redacted] GLP; Unpublished	Y	Thor GmbH
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;	Y	Thor GmbH

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			Unpublished		
III-A 3.13 III-B 3.10	[redacted]	2007	Determination of the surface tension of an aqueous solution of MIT (applied as ACTICIDE® M 20) according to OECD 115 resp. EU A.5; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 4.1-01	[redacted]	2007	Determination of 2-Methyl-4-isothiazoline-3-one (MIT) in biocides; [redacted] Non- GLP; Unpublished	Y	Thor GmbH
III-A 4.1-02	[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	

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			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 to Magnusson and Kligman; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.1.5-02	[redacted]	2002	ACTICIDE M 50 - Local Lymph Node Assay (LLNA) in Mice (Identification of contact Allergens); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.2-	[redacted]	1998	(14C)-CIT and (14C)-MIT: Absorption,	Y	Thor

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01			distribution, metabolism and excretion following oral administration to the rat; [redacted] GLP; Unpublished		GmbH
III-A 6.2-02	[redacted]	2000	(14C)-CIT and (14C)-MIT: Characterisation of metabolites following oral administration to the rat; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.2-02	[redacted]	1982	^{14}C-Kathon 886 disposition after percutaneous application to male rats; Toxicology department, [redacted] 17.12.1982; Unpublished	N	Rohm and Haas
III-A 6.3.1-01	[redacted]	2002	Repeated Dose 28-Day Oral Toxicity Study of ACTICIDE M 50 in Rats; [redacted] Unpublished	Y	Thor GmbH
III-A 6.3.3 III-A 6.4.3	AgBB Evaluation Scheme	2005	A contribution to the Construction Products Directive: Health-related Evaluation Procedure for Volatile Organic Compounds Emissions (VOC and SVOC) from Building Products; http://www.umweltbundesamt.de/building-products/agbb.htm; AgBB - September 2005, Updated List of LCI values 2005 in Part 3; Non- GLP Published	N	n.a.
III-A 6.4.1-01	[redacted]	2002	Repeated Dose 90-Day Oral Toxicity Study of ACTICIDE M 50 in Rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.4-2	[redacted]	2004	2-Methyl-4-isothiazolin-3-one: A 13-week dietary toxicity study in dogs; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.5-01	[redacted]	2007	MIT: Justification for the submission of a chronic toxicity/oncogenicity study estabished on the combination CIT/MIT (3:1) rather than a chronic/oncogenticity study conducted on MIT; [redacted] Non-GLP Unpublished	Y	Thor GmbH
III-A 6.6.1-1	[redacted]	2000	Investigation of Acticide SR 3267 on Mutagenicity by the Reverse Mutation Assay in Salmonella typhimurium (Ames-test); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.6.2-1	[redacted]	2002	In vitro Mammalian Chromosome Aberration Test of ACTICIDE M 50 with Human Lymphocytes; [redacted] GLP; Unpublished	Y	Thor GmbH

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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] 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 6.7-02	[redacted]	1994	24-Month Drinking Water Chronic/Oncogenic study in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.8.1-01	[redacted]	2003	A oral (gavage) developmental toxicity study of 2-Methyl-4-isothiazolin-3-one in rabbits; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A6.8.1.b_01	[redacted]	2003	Stump 01RC-269Bsecured_historical control_Doc III A6.8.1.b_01 rabbit teratogenicity.pdf; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.8.1-02	[redacted]	2000	Teratogenicity study of test item ACTICIDE SR 3267 in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.8.2	[redacted]	2003	A Two-Generation reproductive development toxicity study of 2-Methyl-4-isothiazolin-3-one administered via drinking water in rats; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A6.8.2-01	[redacted]	2003	Stump 01RC-285Bsecured_historical control_Doc III A6.8.2_01_2-generation rat.pdf; [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 6.12-01	[redacted]	2007	Medical data for 2-Methyl-2H-isothiazol-3-one, CAS 2682-20-4; [redacted] Unpublished	Y	Thor GmbH
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	N	

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			materials; The EFSA Journal (2007) 555-563, 1-31; Report Nº: 66755; 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 7.1.3-02	[redacted]	2002	ACTICIDE 14 - Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.2.1	[redacted]	2007	Study for the determination of the degradation of 2-Methyl-2H-isothiazol-3-one (MIT, CAS # 2682-20-4) in soil (OECD 307); [redacted] GLP	Y	Thor GmbH

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			Unpublished		
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] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.1.3-02	[redacted]	2007	Determination of the effect of 2-Methyl-2H-isothiazol-3-one (MIT, CAS# 2682-20-4) on the growth of the marine diatom Skeletoma costatum (International Standard ISO 10253); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.3.2	[redacted]	2006	2-Methyl-2H-isothiazol-3-one (MIT, Applied as Aqueous Formulation ACTICIDE® M 20): An Early Life-Stage Toxicity Test with the Fathead Minnow (Pimephales promelas); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.4.3.4	[redacted]	2006	2-Methyl-2H-isothiazol-3-one (MIT; Applied as Aqueous Formulation ACTICIDE® M 20): A Flow-Through Life-Cycle Toxicity Test with the Cladoceran (Daphnia magna); [redacted] GLP; Unpublished	Y	Thor GmbH
III-A 7.5.1.1-01	[redacted]	2006	An assessment of the effects of 2-Methyl-2H-isothiazol-3-one (MIT, applied as aqueous formulation ACTICIDE® M 20) on the nitrogen transformation and carbon mineralization activity of soil micro-organisms (OECD 216 and 217 guidelines);	No	Thor GmbH

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			[redacted] GLP; Unpublished		
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 Determine the Effects on Seedling, Emergence and Growth of Terrestrial Plants; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 2	[redacted]	2000	ACTICIDE M 20S: 5 Batch Analysis; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.1	Brauch G	2007	SDB_ACTICIDE_M_20_S&A_1002&GB_.pdf; Thor GmbH; Non-GLP; Published	Y	Thor GmbH
III-B 3.5	[redacted]	2000	pH value of Acticide M 20S; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.6	[redacted]	2000	Density of Acticide M 20S; [redacted] Unpublished	Y	Thor GmbH
III-B 3.7	[redacted]	2001	The Storage Stability of Acticide M 20S at 20°C; [redacted] GLP; Unpublished	Y	Thor GmbH
III-B 3.7	[redacted]	2000	Stability of ACTICIDE M 20S to Elevated Temperature; [redacted] [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); [redacted]	Y	Thor GmbH

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			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] GLP; Unpublished	Y	Thor GmbH
III-B 6.3.-02	[redacted]	2005	Skin sensitization of test item Acticide M 10 S in Guinea Pigs by Magnusson and Kligman; [redacted] GLP; Unpublished	Y	Thor GmbH