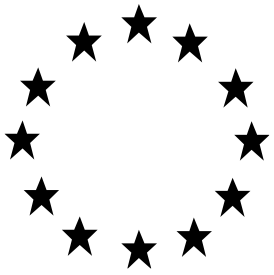
Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



N,N-Methylenebismorpholine

Product-type 6 & 13
(In-can preservative; Metalworking fluid preservative)

November 2014

Austria

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Principle of evaluation

This assessment report has been established as a result of the evaluation of N,N-Methylenebismorpholine as product-type 6 & 13 (In-can preservative, Metalworking fluid preservative), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market1, with the original view to the possible inclusion of this substance into Annex I or IA to that Directive.

The evaluation has therefore been conducted in the view to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product-type 6 containing N,N-Methylenebismorpholine that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that Directive. Those requirements and common principles are very similar to those laid down in Article 19(1), (2) and (5) and Annex VI of Regulation (EU) No 528/2012. At the time of finalisation of this assessment report, there was no indication that the conclusions regarding compliance with Directive 98/8/EC would not be valid for the purpose of establishing compliance with the requirements of Regulation (EU) No 528/2012.

1.2. Purpose of the assessment

The aim of the assessment report is to support a decision on the approval of N,N-Methylenebismorpholine for product-type 6, and should it be approved, to facilitate the authorisation of individual biocidal products in product-type 6 & 13 that contain N,N-Methylenebismorpholine. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Regulation (EU) No 528/2012.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report shall be taken into account.

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

1.3. Procedure followed

This assessment report has been established as a result of the evaluation of N,N-Methylenebismorpholine as product-type 6 & 13 (In-can preservative, Metalworking fluid

1 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

preservative), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market.

N,N-Methylenebismorpholine (CAS no. 5625-90-1) was notified as an existing active substance, by Lubrizol Deutschland GmbH, Metalworking Additives, hereafter referred to as the applicant, in product-type PT 6 & 13.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, CA was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for N,N-Methylenebismorpholine as an active substance in Product Type 6 and 13 was 31st July 2007, in accordance with Article 9 (c) of Regulation (EC) No 1451/2007.

On 1st August 2007, Austrian competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 30 January 2008.

On 25 July 2013, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 31 July 2013. The competent authority report included a recommendation for the inclusion of N,N-Methylenebismorpholine in Annex I to the Directive for product-type PT6 & 13.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on [date]. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

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 Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on [date].

2 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

2. OVERALL SUMMARY AND CONCLUSIONS

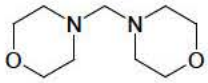
Remark: For data on formaldehyde, please refer to the formaldehyde Core Dossier.

2.1. Presentation of the Active Substance

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

The active substance N,N-Methylenebismorpholine (short: MBM) is attributed the CAS-No 5625-90-1 and the EC-No 227-062-3. The molecular formula is $C_9H_{18}N_2O_2$, and the molecular weight is 186.26 g/mol. The minimum degree of purity is 92.1%w/w.

Structural formula:



The structure of N,N-Methylenebismorpholine is confirmed by all spectra (IR, NMR, UV/VIS and MS).

Physico-Chemical Properties of the Active substance:

The physico–chemical properties are studied for the active substance of stated specification (min. 92.1%w/w N,N-Methylenebismorpholine [short: MBM]) according to the demands of the data requirements.

MBM is a pale yellow liquid, has a slightly amine like odour. Its melting point range is 18 - 21°C, and the boiling point is 266.4°C. The relative density is 1.05 at 20°C and the density is 1.0647 g/cm^3 at 20°C. The calculated vapour pressure of the active substance is 0.625 Pa at 25°C (EpiSuite) and 0.443 at 20°C (conversion of the Episuite value to 20°C by EUSES). The calculated Henry's law constant is 2.72x10^{-5} Pa m^3 mol^{-1} at 25°C. Water solubility cannot be determined as the active substance is hydrolysable. MBM is miscible in water in all proportions (at 10 - 30°C and at pH 5 - 9).

The dissociation constant (pKa) is calculated to be 7.39 and 2.98 at 20°C. (MBM cannot be isolated because of its hydrolysis properties and therefore determination of the single pKa values is not possible.) The solubility of MBM is 2000 – 2500 mg/L in Heptan and MBM is completely miscible in DMSO, Toluene, Ethanol, n-Octanol, Acetone and partially soluble in Cyclohexane at 21-23 °C. (Concentrations tested: 5000, 2500, 1000, and 500 mg/mL)

The active substance as manufactured does not contain any organic solvents. The calculated partition coefficient Octanol-Water is -1.53, the measured log Pow ≤ 0.3 (hydrolysed test substance; pH: 5, 7, 9 at 30°C).

The surface tension cannot be determined due to hydrolysis in aqueous solution. The viscosity is 16 mPas at 20°C.

The active substance MBM displays neither explosive nor oxidizing properties based on its structure. Its flash point is 115°C. The substance can be safely handled up to its flash point (115°C). It is not considered to be reactive to container material (LDPE.).

Physico-Chemical Properties of the Hydrolysis product Morpholine:

Morpholine is a hydrolysis product of the active substance N,N-Methylenebismorpholine
Selected literature data on physico–chemical properties were provided by the applicant:

Morpholine is an oily ,hygroscopic, colourless liquid; has a characteristic amine smell. Its melting point range is -3,1 to -5°C, and the boiling point is 128°C. The relative density is 1.0001 at 20°C.The vapour pressure of morpholine are 1.1 kPa at 20°C; 3.2 kPa at 40°C and 1.34 kPa at 25°C
The literature data of Henry's law constant are 49 Pa m^3 mol^{-1}(20°C); 244 Pa*m^3*mol^{-1} and
0.012 Pa*m^3*mol^{-1}(25°C) The structure of morpholine is confirmed by IR- spectra.

Morpholine is miscible with water and has a low soluble in alkaline aqueous solutions. The dissociation constant (pKa) is to be 8.5 and 8.33 at 25°C. Morpholine is completely miscible with, for instance, methanol, ethanol, acetone, diethyl ether, benzene, toluene, xylol.
The partition coefficient Octanol-Water is -0.86 (pH no data), and -2.55 (pH 7). Morpholine is not surface active and the viscosity is 2.021 mPas at 25°C.

The hydrolysis product morpholine displays neither explosive nor oxidizing properties based on its structure.Its flash point is 38°C- Open cup and 33°C - Closed cup.
Morpholine is a flammable liquid Category 3.
It is not considered to be reactive to container material (LDPE.).

Analytical Methods:
The active substance N,N-Methylenebismorpholine as manufactured is in equilibrium with the starting materials. Because of the dynamic nature of the equilibrium analytical standard methods like HPLC/UV, LC/MS, GC/MS, photometry are difficult to use for characterisation of the composition and the determination of the active-ingredient-content or the impurities.

The content of the active substance N,N-Methylenebismorpholine and its organic impurities has been determined by NMR-analysis using ^{1}H- and ^{13}C-NMR techniques. The remaining inorganic impurity has been determined by titration method.

The method has been validated and shown to be sufficiently specific, accurate and sensitive.

2.1.2. Intended Uses and Efficacy

N,N-Methylenebismorpholine containing biocidal products are used as bactericides for the preservation of fuels (PT6) and metal working fluids (PT13) which are prone to bacterial decay. Two out of seven studies submitted were suitable for proof of preservation, whereas the remaining five studies, which also covered mycobacteria and fungi, were rather suitable for proof of disinfection properties.

The active substance is a formaldehyde-releaser. The biocidal activity of the active substance is due to the interaction of the released formaldehyde with protein, DNA and RNA. The interaction with protein results from a combination with the primary amide and the amino groups. It reacts with carboxyl, sulfhydryl and hydroxyl groups.

As formaldehyde is not specific for one cellular target the development of resistances is not to be expected.

For applications in PT 6 the product is intended to be incorporated by industrial users into fuels during the formulation process, which is carried out automatically, to act as a preservative with bactericidal activity. Formulation is performed in closed systems and high degree of automation resulting in a final concentration of the active substance of concentration of 0.01-0.1% in the fuel.

For applications in PT 13 (Metalworking fluid preservative) the product is intended to be incorporated by professional users into water based emulsifiable metalworking fluids (MWF) to act as a preservative with bactericidal activity. The lubricant concentrate, intended for the preparation of water based emulsifiable metal working fluids, contains the active substance at a concentration of 3% w/w. The use concentration of the active substance in metalworking fluids is typically 0.15% w/w. The active substance has to be regularly or occasionally re-dosed if a.s. is below effective concentration of 0.15% w/w.

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against gram negative bacteria such as *Citrobacter freundii, Alcaligenes faecalis, Pseudomonas aeruginosa* and *Enterobacter aerogenes*).

2.1.3. Classification and Labelling of the active substance

Current classification according to Annex VI of Reg. (EU) No 1272/2008

For the active substance there is no harmonised classification available in Annex VI of Reg. (EU) No 1272/2008. For the hydrolysis products Morpholine and Formaldehyde there are harmonised classifications available in Annex VI of Reg. (EU) No 1272/2008 and in the 6. ATP to Reg. (EU) No 1272/2008, respectively.

Classification is to be decided by RAC and COM. Proposal 1 will be submitted together with supportive arguments. Also proposal 2 will be discussed by respectively supportive arguments (see table 2.1.3-1, below).

Table 2.1.3-1: Discussion with regard to carcinogenicity and genotoxicity

supportive arguments for proposal 1:	**supportive arguments for proposal 2:**
Classification according to releasable formaldehyde, i.e. Skin Corr. 1, Skin Sens 1, Carc. 1B	Classification according to “free formaldehyde”, i.e. Skin Corr. 1
Risk through formaldehyde-release in water is covered	Classification usually relates to the substance itself and not to potential release or degradation products which occur during different use scenarios
The formaldehyde releaser is difficult to characterise since it shows equilibrium behaviour and having half-lives depending on dilution, temperature and pH.	Analogue to the evaluation of other “substances of concern” or impurities the cut-off values from the GHS system should be considered for the real amount of free formaldehyde
If classification considers the handling, the dilution and the release kinetics should be considered as well: The DT50 of the release was measured as 2.4 hours at 50°C and probably also at 37°C (study documentation is limited for the latter). Each mg MBM releases 0.16 mg	Formaldehyde -releasers are designed as transport forms and depot compounds and these benefits of slow continuous formaldehyde release should be considered. Formaldehyde releasers should not be equalized with a pure formalin-solution.

formaldehyde Formaldehyde release is a hydrolysis and occurs with contact with biological tissue and media	
Solutions of formaldehyde releasers only need to be classified if formaldehyde content is above 0.1%	Formaldehyde release is a hydrolysis and occurs in dilutions with water → depending on the releaser type this needs dilutions between 1:10 and 1:1000
In vitro genotoxicity data for MBM support the assumption of <u>local</u> genotoxicity and consequent <u>local</u> carcinogenicity	Other examples for substances (oligomers) that contain formaldehyde and are classified according to free formaldeyhde: ● Polyoxymethylen (CAS formaldehyde-polymer = technical plastic) has different properties compared to FA and is classified differently ● Paraformaldehyde itself (degree of polymerization of 8–10 units) is only classified as toxic (T) and corrosive (C) so far Instead of full classification and labelling a warning label could be applied „can release FA with water contact“ A classification of formaldehyde-releasers on the basis of maximal releasable formaldehyde could be considered as an unusual mixture between the classification process and risk assessment which does not justify either of the both procedures

The applicant summarized the following consequences of classification according to maximal releasable formaldehyde (proposal 1):

- Classification and labelling implies a lot additional requirements for storage and transport
- High protection measures need to be implemented (e.g. respiratory protection at refilling) also in cases where only a low risk is existent (no water contact)
- Possible products and uses will be impossible on the market due missing users acceptance (panics); as a last consequence a whole group of substances showing a high and broad efficacy could disappear from the market and will be replaced by other products showing other problems which presumably do not have a comparable efficacy

For environmental effects C&L according to Regulation (EC) No 1272/2008, Annex VI, Table 3.1 and Regulation (EU) No 286/2011 is not necessary, since neither the active substance (MBM), nor the hydrolysis products (formaldehyde and morpholine) fulfil the classification and labelling criteria.

Table 2.1.3-2 **Proposal 1** for classification of MBM **by the RMS** according to Reg. 1272/2008/EC

Classification		**Justification**
Classification	Skin Corr. 1 Skin Sens. 1 Carc. 1B Muta 2	See below
	H314: Causes severe skin burns and eye damage	rabbit test results
	H317: May cause an allergic skin reaction	consideration of use phase of substance: FA* release by contact with biological media and dilution
	H350: May cause cancer	consideration of use phase of substance: FA* release contact with biological media and dilution
	H341: Suspected of causing genetic defects	consideration of use phase of substance: FA* release contact with biological media and dilution

Table 2.1.3-3 **Proposal 1** for labelling of MBM **by the RMS** according to Reg. 1272/2008/EC

Labelling	
GHS Pictograms	
Signal words	Danger
	H314: Causes severe skin burns and eye damage
	H317: May cause an allergic skin reaction
	H350: May cause cancer
	H341: Suspected of causing genetic defects
Precautionary Statements	To be completed after decision for classification

Table 2.1.3-4 **Proposal 2** for classification of MBM **by the applicant** according to Reg. 1272/2008/EC (changes to proposal 1 shaded in grey, deletions crossed out)

Classification		**Justification**
Classification	Skin Corr. 1 ~~Skin Sens. 1~~ ~~Carc. 1B~~ ~~Muta 2~~	See below
	H314: Causes severe skin burns and eye damage	rabbit test results
	~~H317: May cause an allergic skin reaction~~	Formal consideration of substance at the time being "supplied to the user" (FA content < 0.1%)
	~~H351: Suspected of causing cancer by inhalation~~	Formal consideration of substance at the time being "supplied to the user" (FA content < 0.1%)
	~~H341: Suspected of causing genetic defects~~	Formal consideration of substance at the time being "supplied to the user" (FA content < 0.1%)

Table 2.1.3-5 **Proposal 2** for labelling of MBM **by the applicant** according to Reg. 1272/2008/EC (changes to proposal 1 shaded in grey, deletions crossed out)

Labelling	
GHS Pictograms	
Signal words	Danger
	H314: Causes severe skin burns and eye damage
	~~H317: May cause an allergic skin reaction~~
	~~H351: Suspected of causing cancer by inhalation~~
	~~H341: Suspected of causing genetic defects~~
Precautionary Statements	To be completed after decision for classification

2.1.4. Classification and Labelling of the biocidal product for PT 6 and PT 13

Proposed classification and labelling

The representative biocidal product is identical to the active substance as manufactured and is marketed as CONTRAM™ ST-1.

Therefore for classification and labelling of the biocidal product according to Regulation (EC) No 1272/2008, Annex VI reference is made to the classification and labelling of the active substance above.

2.2. Summary of the Risk Assessment

2.2.1. Risk arising from physico-chemical properties

The active substance displays neither explosive nor oxidizing properties. Its flash point is 115°C. In conclusion, no physico-chemical hazards and therefore also no risk could be identified for the active substance.

2.2.2. Human Health Risk Assessment

2.2.2.1. Hazard identification

The toxicokinetic studies available for MBM, the in vitro dermal absorption study and the intra-tracheal instillation study support in qualitative terms that MBM hydrolyses to formaldehyde and morpholine upon contact with biological tissues. Within the toxicological studies MBM induces only local effects and in some studies additionally effects that are considered as secondary to local effects. The substance is corrosive to skin (and eye), acute (oral) toxicity seems to be due to the corrosive properties. In repeated dose gavage studies in rats (90 day study) and rabbits (developmental toxicity study) only local effects in the stomach were detected with very similar LOAECs of 2.5% and 3%, respectively, and NOAECs of 0.75 and 1% and systemic NOAELs above 100 mg/kg bw day. Reduced food consumption and reduced body weight gain observed in the developmental toxicity study are considered as secondary to the local effects.

The available guinea pig maximisation test is inconclusive since tested concentrations were too low. Nevertheless MBM has to be considered as skin sensitizer on the basis of the mechanistic consideration of formaldehyde release upon contact with biological tissues. MBM results clearly positive within bacterial gene mutation tests, an in vitro chromosomal aberration test and an in vitro gene mutation test. The in vivo mouse micronucleus and rat UDS tests are negative. No carcinogenicity study and no specific fertility study are available for MBM.

However the toxicological profile of MBM and the respective hydrolysis study data provide sufficient evidence to read across the local effects data from formaldehyde to MBM. The toxicity of MBM is dominated by local irritation and local (in vitro) but not systemic genotoxicity, the toxicokinetic studies support in qualitative terms what is expected from the hydrolysis study and efficacy mode of action: The equilibrium of MBM and formaldehyde quickly shifts towards formaldehyde and morpholine by dilution and by the reaction of formaldehyde with biological media.

The hazard profile of formaldehyde was evaluated by the RMS DE (CAR submission in August 2013) and should serve as the agreed reference. For morpholine predominantly

local effects were observed. A summary of the hazard assessment is available in the respective appendix to the CAR.

2.2.2.2. Effects assessment

Consequently in the absence of inhalation studies with MBM the local respiratory AEC of formaldehyde (0.12 µg/L air) derived from human data is read across to MBM (0.75 µg/L air) on a molar basis. No local dermal AEC can be derived due to the sensitizing properties of MBM, but the classification limits of formaldehyde for skin sensitization (0.2%) read across to MBM (1.2%) or the general classification limit for skin sensitization (1%) and the default classification limit for skin irritation (1%) can be engaged for a qualitative risk characterisation. Oral AECs are not relevant for the intended applications.

In contrast a systemic short medium and long term AEL can be derived from data generated with the active substance on the basis of a NOAEL at the highest dose tested in the sub-chronic study (> 150 mg/kg bw) and application of the standard assessment factor of 100 for interspecies and intra-species uncertainty as well as an addition factor of 2 for extrapolation from sub-chronic to chronic exposure scenarios (> 0.75 mg/kg bw day). This AEL is in the same range as the short, medium and long term AEL derived for formaldehyde (0.15 mg/kg bw day) and the long term AEL derived for morpholine (0.77 mg/kg bw day) if read across on a molar basis.

In the context of the classification of formaldehyde for carcinogenicity category 1B RAC3 considered that the data available for formaldehyde in the low dose range may not be sufficiently reliable to support a threshold assumption and standard assessment factors for deriving a DNEL (AEL) for risk assessment. Derivation of a DMEL should be considered. However formaldehyde substance evaluation for REACH is ongoing and it is expected that acceptable exposure level estimates will also be provided and discussed in this context. Furthermore RAC evaluation of the CLH Dossier for MBM with regard to carcinogenicity is ongoing. Therefore the BPC-WG in June 2014 supported to use the AEL values provided and agreed in the formaldehyde core dossier (eMS: DE) for the approval of the formaldehyde releaser MBM.

The REACH and RAC evaluations (including DNEL or DMEL for formaldehyde; C&L for MBM) will be considered when available, at product authorisation stage or for the renewal of the active substance (i.e. 5 years after Union List inclusion, see also opinion table of MBM, chapter 2.3.).

2.2.2.3. Exposure assessment

Product type 6 (in can preservatives)

Human exposure towards the active substance from its use in the biocidal product can take place via different “routes of exposure”, i.e. *via* inhalation, dermal contact and/or ingestion (see table 2.2.2.3-1).

Table 2.2.2.3-1: Main paths of human exposure to MBM

Exposure path	Primary (direct) exposure, during use of b.p.	Secondary (indirect) exposure Incidental contact after	Via the environment[1]

3 RAC Opinion proposing harmonised classification and labelling at EU level of formaldehyde; CLH-O-0000003155-80-01/F; adopted 30 November 2012

			application	
	Professional use	**General public**	**General Public**	**General Public**
Inhalation	Yes	Yes	Yes	Yes[1]
Dermal	Yes	Yes	Not relevant	Not relevant[1]
Oral	Not relevant	Not relevant	Not relevant	Not relevant[1]

[1] From TNsG on Human Exposure, 2007: "Exposure via the 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.

The active substance MBM is used for the preservation of fuels (PT 6).

Most sites apply MBM in closed systems using automatic dosage during formulation of fuels. As fuels represent mainly an organic matrix and no addition of water is intended, hydrolysis of MBM and formation of formaldehyde and exposure to formaldehyde is expected to be of minor relevance (due to maximal 0.05% amount of water in the fuel, the amount of fuel-releasable formaldehyde is extremely low). Therefore, exposure to the hydrolysis product formaldehyde was not considered regarding this use.

Formulation of fuels is not performed by non-professionals, therefore, human exposure of the general public via this application is considered to be not relevant. Anyhow professional and non-professional contact with the active substance might take place during refuelling of engines. Further exposure is not expected due to the combustion of MBM within the engines. Indirect exposure of the general public is considered to be only relevant via the inhalational route (e.g. bystanders during refuelling an engine). Dermal (and oral) contaminations are not expected for persons, who are not handling the fuel by themselves.

Also combined exposure (i.e. total exposure via all exposure routes arising from individual tasks through different phases of use), as well as aggregate exposure (i.e. exposure to a single chemical from multiple sources i.e. through primary exposure and secondary exposure) were assessed/regarded. Cumulative exposure which covers concurrent exposure to the same active substance from different biocidal products was not evaluated at present for MBM.

Exposure of pets is not considered to be relevant based on the intended use.

Dietary exposure is not considered to be relevant on the intended use.

The exposure values relevant for risk characterisation are presented in chapter 2.2.2.4 of this document.

Product type 13 (metal working fluids)

The area primary exposure of professionals covers workers, who prepare lubricant concentrates and workers, who prepare/apply metal working fluids. Referring to the identified tasks, inhalation and dermal exposures of workers are considered to be relevant (see table 2.2.2.3-2).

The lubricant concentrates and the metalworking fluids contain significant amounts of water and MBM hydrolyses quickly, therefore, total transformation of MBM to formaldehyde and morpholine seems to be an acceptable assumption. As formaldehyde reveals a higher toxicity and volatility than morpholine, the calculations target only

formaldehyde. Exposure to morpholine is considered to be covered under these circumstances.

As the pure biocidal product and the lubricant concentrate are not intended for non-professionals, exposure of the general public via primary respectively secondary exposure are not considered.

Table 2.2.2.3-2: Main paths of human exposure to MBM/formaldehyde

Exposure path	**Primary (direct) exposure, during use of b.p.**		**Secondary (indirect) exposure Incidental contact after application**	**Via the environment[1]**
	Professional use	**General public**	**General Public**	**General Public**
Inhalation	Yes	Not relevant	Not relevant	Not relevant[1]
Dermal	Yes	Not relevant	Not relevant	Not relevant[1]
Oral	Not relevant	Not relevant	Not relevant	Not relevant[1]

[1] From TNsG on Human Exposure, 2007: “Exposure via the 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.

Preparation of lubricant concentrates is performed by professionals at industrial sites using the the biocidal product. Most formulation sites reveal closed systems and automatic compound dosage installations. Nevertheless, dermal contact and inhalation exposure cannot be fully excluded.

Metalworking processes include several potential exposure scenarios like mixing and loading, machine work (drilling, grinding, tool settling and dismantling, etc.), control and cleaning of work pieces, etc. These tasks are performed by professionals. Referring to the intended use, machine work is performed in closed chambers preventing contamination of workers. The degree of prevention differs significantly based on the installations at place. Closed chambers do not represent a fully closed system in most cases. Therefore, the presence of aerosols and gaseous releases in air needs to be considered. Referring to the covered tasks, inhalation and dermal exposures of workers were estimated.

Combined exposure (i.e. total exposure via all exposure routes arising from individual tasks through different phases of use) was assessed. Secondary and aggregate exposure (i.e. exposure to a single chemical from multiple sources i.e. through primary exposure and secondary exposure) were expected to be not relevant. Cumulative exposure which covers concurrent exposure to the same active substance from different biocidal products was not evaluated at present for MBM.

Exposure of pets is not considered to be relevant based on the intended use.

Dietary exposure is not considered be relevant on the intended use.

The exposure values relevant for risk characterisation are presented in chapter 2.2.2.4 of this document.

2.2.2.4. Risk characterisation

Product type 6 (in can preservatives)

The risk from the application of the biocidal product CONTRAM™ ST-1 to the fuel (**PT6, in can preservative**) within industrial processes and the use of the treated fuel by professionals and by general public is characterised in this CAR. Due to the low content of water in fuel the active substance is considered as largely non-hydrolysed. Consequently **the risk is characterised on the basis of exposure estimates and toxicological reference values for the active substance only**.

The risk from respiratory exposure to CONTRAMTM ST-1 from application to fuel appears only acceptable with very effective local exhaust ventilation systems in place, respective exposure model results support an acceptable risk for local respiratory effects.

Table 2.2.2.4_1 Risk for local respiratory effects: Application of CONTRAMTM ST-1 to fuel

Exposure Scenario: Addition of CONTRAM™ ST-1 to dosage systems or fuel in formulation vessels, sampling for formulation control		Local (external) respiratory exposure estimate [mg/m³]	Local respiratory AEC [mg/m³]	Local respiratory exposure / AEC
Tier 1	Consexpo-model estimate, tier 2, reasonable worst case	0.062	0.75	0.08

Table 2.2.2.4_2 Risk assessment for **local** dermal effects: Application of CONTRAM™ ST-1 to fuel in formulation vessels

Hazard			Exposure							Risk
Hazard Category	effects in terms of C&L	additional relevant hazard information	PT	Who is exposed?	Tasks, uses, processes	Potential exposure route	frequency and duration of potential exposure	Rough degree of exposure	Relevant RMM & PPE	Conclusion on risk
high	Cat 1, H314: severe skin burns and eye damage Cat 1, H317: may cause allergic skin reaction	classification limits: 5% (corrosion) 1% (sensitization) respiratory AEC = 0.75 µg/L air	6	industrial	most formulation sites have closed systems using automatic dosage systems: **addition of CONTRAM ST-1 to the dosage system or directly to fuels**;	Skin Eye RT	few minutes per day or less	n.r.	Technical and organisational RMM adequate for the high hazard category are achievable transfer in closed systems and industrial RMM excluding risk for skin, eye and RT exposure use of appropriate gloves and mask	Acceptable: No exposure expected since +Technical and organisational RMM adequate for the high hazard category are achievable
no	-	Concentration of 0.1% in fuel is ≤ class limits for corrosion (5%), irritation (1%) and skin sensitization (1%) respiratory AEC = 0.75 µg/L air	6	industrial	most formulation sites have closed systems using automatic dosage systems: **sampling of fuel for**	Skin Eye RT	few minutes per day or less	n.r.	Technical and organisational RMM of standard industrial work place may be expected. use of gloves recommended	Acceptable: No hazard classification

control

n.r. = not relevant

In addition to the critical local effects also potential systemic effects were estimated. The respective risk ratios are below 1, indicting an acceptable risk for systemic combined respiratory and dermal exposure with 10% penetration through gloves, including the tasks addition of CONTRAMTM ST-1 to dosage systems or fuel in formulation vessels and sampling for formulation control.

Table 2.2.2.4_3 Risk for **systemic** effects from the application of CONTRAM ST-1 to fuel in formulation vessels

Exposure Scenario: Addition of CONTRAM™ ST-1 to dosage systems or fuel in formulation vessels, sampling for formulation control		Systemic (internal) exposure [mg/kg bw day]				Systemic AEL [mg/kg bw day]	Systemic exposure / AEL
		oral	inhalation	dermal	total		
Tier 2	Respiratory exposure Consexpo- model estimate (tier 1, reasonable worst case) and Dermal exposure to treated fuel from sampling, tier 2, including 10% penetration through gloves (see Doc II-B.4.1.3)	n.r.	0.01	0.0029	0.013	0.75	0.017

n.r. not relevant

The risk from respiratory exposure to CONTRAMTM ST-1 by refuelling of engines with treated fuel appears only acceptable with very effective local exhaust ventilation systems in place, respective exposure models support an acceptable risk for local respiratory effects.

Table 2.2.2.4_4 Risk for **local** respiratory effects: Use of fuel treated with CONTRAM™ ST-1 - refuelling of engines.

Exposure Scenario: Refuelling of engines		Local (external) exposure [mg/m³]	Local respiratory AEC [mg/m³]	Local respiratory exposure / AEC
Tier 1	Respiratory exposure Consexpo model estimate	0.056	0.75	0.075

Dermal exposure to treated fuel should be avoided, also due the potentially sensitizing property of the active substance. However the concentration of CONTRAM ST-1 in fuel is 0.1%, which is below the classification limit for skin irritation (1%) and for skin sensitization (1%) indicating a low risk for local dermal effects from acute (occasional) dermal contact with treated fuel. In addition to the critical local effects also potential systemic effects were estimated for professionals. This dermal to systemic exposure estimate not taking into consideration the use of gloves was combined with an inhalation

to systemic exposure estimate and indicated a systemic risk ratio below 1, i.e. an acceptable risk. This estimate covers also risk for general public refuelling their engines as well as bystanders including children and pet animals.

Table 2.2.2.4_5 Risk for **systemic** effects from the professional use of fuel treated with CONTRAM™ ST-1 – refuelling engines by professionals

Exposure Scenario: Refuelling engines by professionals		Systemic (internal) exposure [mg/kg bw day]				Systemic AEL [mg/kg bw day]	Systemic exposure / AEL
		oral	inhalation	dermal	total		
Tier 1	Respiratory exposure Consexpo model estimate and Dermal exposure to a.s. tier 2, no gloves (see Doc II-B.4.1.3)	n.a.	0.01	0.042	0.052	0.75	0.07

n.a. not applicable

Product type 13 (metal working fluids)

With the application of CONTRAM™ ST-1 to **metal working fluids (PT13)** MBM will at least partly hydrolyse to formaldehyde and morpholine. Consequently the risk is may be characterised considering the two most extreme situations: Non-hydrolysed MBM or 100% hydrolysis to formaldehyde and morpholine. As explained above the AECs and AELs of MBM and the hydrolysis products are on a molar basis concordant with each other. However with regard to exposure formaldehyde can be considered as the most critical component, since it´s vapour pressure and Henry law constant are highest and the dermal absorption rates are similar. This leads to slightly higher exposure estimates for formaldehyde. Consequently **the risk from the active substance within product type 13 (metal working fluid) could be characterised by assuming complete hydrolysis and assessment of just formaldehyde as the most critical component**. Just in case this approach would indicate an unacceptable risk it could be investigated if a refinement is possible, by respecting the state of hydrolysis in the various scenarios and the specific vapour pressure for the active substance and the hydrolysis products. However this was neither necessary nor useful for the actual assessment.

The use of CONTRAMTM ST-1 in metal working processes can lead to exposure from the tasks mixing and loading CONTRAM™ ST-1 or a lubricant concentrate to the metal working fluid, machine work, control and cleaning of work pieces, fluid monitoring, swarf removal and discharging the system. Risk for potential local respiratory effects from these tasks can be modelled with reference measurements indicating formaldehyde exposure of 0.007 mg/m³. This is below the AEC of 0.12 mg/m3, indicating an acceptable risk for the critical local respiratory effects.

Table 2.2.2.4_6 Risk for **local** respiratory effects from formaldehyde via CONTRAM ST-1

Exposure Scenario: Application of CONTRAM ST-1 or lubricant concentrates to metal working fluids		Local respiratory exposure to formaldehyde [mg/m³]	Local respiratory AEC [mg/m³]	Local respiratory exposure / AEC
Tier 2	Inhalation: measured data for metal working fluids in working environment	0.007	0.12	0.06

Dermal exposure to the product CONTRAM ST-1 has to be completely excluded by the use of appropriate piping technology due to its skin corrosive and skin sensitizing properties. Dermal exposure to the lubricant concentrate, a dilution of the product (3% a.s.~0.5% formaldehyde), should be avoided at least with appropriate personal protective equipment due to its irritating and skin sensitizing properties. Dermal exposure to the treated mwf (0.15% a.s.~0.024% formaldehyde) should also be avoided due to the skin sensitizing properties though formaldehyde concentrations are below the classification limit for skin sensitization (0.2%). It is concluded that manual mixing and loading of CONTRAM ST-1 to metal working fluid presents an unacceptable risk for local dermal effects, taking into consideration the potential severity of effects and the possibilities to prevent them with automated systems. However it is concluded that with automated systems of mixing and loading of CONTRAM ST-1 the complete process, including all tasks presents an acceptable risk for local dermal effects.

Table 2.2.2.4_7: Risk for **local** dermal effects from CONTRAM ST-1 – addition to metal working fluid

Hazard			Exposure							Risk
Hazard Category	effects in terms of C&L	additional relevant hazard information	PT	Who is exposed?	Tasks, uses, processes	Potential exposure route	frequency and duration of potential exposure	Rough degree of exposure	Relevant RMM & PPE	Conclusion on risk
high	Cat 1, H314: severe skin burns and eye damage Cat 1, H317: may cause allergic skin reaction	classification limits: 5% (corrosion) 1% (sensitization) respiratory AEC = 0.75 µg/L air	6	Industrial worker	**manual addition of CONTRAM ST-1** to metal working fluid via manholes: opening of vessel, weighting CONTRAM ST-1, addition to metal working fluid and stirring	Skin Eye RT	1x per month: 5-30 min	n.r.	Technical and organisational RMM adequate for the high hazard category Industrial RMM including minimization of manual phases, high ventilation and use of appropriate gloves and face shield allowing to exclude risk for skin, eye and RT exposure	Not acceptable: - Irreversible or severe effect - higher degree of operational and organisational RMM applicable - task is of high frequency
high	Cat 1, H314: severe skin burns and eye damage Cat 1,	classification limits: 5% (corrosion) 1% (sensitization)	6	Industrial worker	**closed dosage system addition of CONTRAM ST-1** to metal	Skin Eye RT	1x per month: 5-30 min	n.r.	Technical and organisational RMM adequate for the high hazard category Industrial RMM including minimization of manual phases and high ventilation allowing to	Acceptable: No exposure expected since + high degree of operational and organisational RMM in use and

	H317: may cause allergic skin reaction	respiratory AEC = 0.75 µg/L air			working fluid			exclude risk for skin, eye and RT exposure use of appropriate gloves and face shield	recommended + short duration and low frequency of potential exposure

Table 2.2.2.4_8: Risk for **local** dermal effects from lubricant concentrate – addition to metal working fluid

medium	Cat 1, H317: may cause allergic skin reaction Cat 2, H315: skin irritation	Lubricate concentrate = 3% a.s; ~ 0.5% formaldehyde , below formaldehyde class limit for irritation: 1% above formaldehyde class limit for sensitization: 0.2% respiratory AEC = 0.75 µg/L air	6	Industrial worker	**manual addition of** **lubricant concentrate** to metal working fluid via manholes: opening of vessel, weighting lubricant concentrate, addition to metal working fluid and stirring	Skin Eye RT	1x per month: 5-30 min	n.r.	Technical and organisational RMM adequate for the medium hazard category Industrial RMM including minimization of manual phases, high ventilation and use of appropriate gloves and face shield allowing to minimize risk for skin, eye and RT exposure	Acceptable: + medium hazard level due to dilution close to irritation and sensitization classification limits + sufficiently high degree of operational and organisational RMM in use and recommended + short duration and low frequency of potential exposure

Risk for local dermal effects from exposure to treated metalworking fluid is considered acceptable, since the concentration of MBM in the metal working fluid is below the classification limit for skin irritation and skin sensitization. Furthermore for several tasks use of coveralls and gloves is expected for protection against mechanical injury.

In addition to the critical local effects also potential systemic effects from respiratory and dermal exposure to lubricant concentrate and mwf were estimated based on reference measurements for respiratory exposure and exposure models for dermal exposure. Dermal exposure to CONTRAM ST-1 was excluded due to the corrosive and sensitizing properties and necessary and available risk mitigation measures. The respective risk ratio is below 1, indicating an acceptable risk for combined respiratory and dermal exposure including the tasks mixing and loading, machine work, control and cleaning of work pieces, fluid monitoring, swarf removal and discharging the system.

Table 2.2.2.4_9. Risk for systemic effects from formaldehyde via Contram ST-1: use in metalworking processes

Exposure Scenario: mixing and loading; machine work; control and cleaning of work pieces; fluid monitoring; gathering shavings/ chippings/ turnings; discharging of system		Systemic (internal) exposure to formaldehyde* [mg/kg bw day]			Systemic AEL for formaldehyde* [mg/kg bw day]	Systemic exposure / AEL
		Inhalation	dermal	total		
Tier 2	Systemic exp. via inhalation assuming 8 hour metal work processes and efficient LEV and Dermal exposure tier 2 and tier ; including gloves protected exposure to lubricant concentrate (10% penetration rate) and no gloves protected	0.001	0.135	0.136	0.15	0.9

	exposure to the treated mwf (see Doc II-B.4.2.4)					

* risk can be characterised with formaldehyde only, see explanation in chapter 1.3.1.

This systemic exposure estimate is most likely an overestimate of real exposure. Considering dermal absorption in terms of conservative flux estimates (that allow correcting the % dermal absorption rate for exposure concentration and time) a total dermal uptake of 0.017 mg/kg bw day was calculated which would result in a risk ratio of 0.12. However the BPC-WG meeting in June 2014 did not agree to this latter approach.

No exposure of general public, no exposure of pets and no dietary exposure is expected due to the intended use in metal working fluids. Dermal contact against dried concentrates in dirty clothes in home laundry of working clothes is assumed to be not relevant as MBM-residues will quickly hydrolyse and generate gaseous formaldehyde, which is transferred to the gaseous phase and will not remain on the clothes.

2.2.3. Environmental Risk Assessment

2.2.3.1. Fate and distribution in the environment

Biodegradation:

Ready and inherent biodegradability:

N,N-**methylenebismorpholine (MBM)** is readily biodegradable (93% degradation after 28 days based on CO_2 measurements) . MBM hydrolysis very quickly (DT_{50} << 1day), therefore the degradation products morpholine and formaldehyde are considered as the substances of interest and the test result can be attributed to the parent compound as well as to the hydrolysis products.

Morpholine is readily biodegradable based on DOC measurements with >90% degradation after 28 days (elimination in the abiotic control was <5%; lag period about 15 days). In an additional inherent test (Zahn-Wellens) a DOC removal >90% was measured after 31 days.

Formaldehyde is readily biodegradable fulfilling the 10-d window.

Degradation in waste water:

Species capable of degrading **morpholine** belong to the genera *Mycobacterium* and *Arthrobacter*. The growth rate of organisms belonging to the genus *Mycobacterium* is very low. Therefore morpholine biodegradation usually features a lag-phase of >14 days. As a consequence the sludge retention time in the STP needs to be long to ensure degradation of morpholine. Adapted STP will remove morpholine without any lag phase.

In STP simulation tests **formaldehyde** was removed to 99.5% under aerobic conditions. It was also rapidly removed under anaerobic conditions.

Abiotic degradation:

Hydrolysis:

Hydrolysis of **N,N'-methylenebismorpholione** is very rapid. No MBM could be detected after 0 and 2.4h at 50°C. Therefore at 25°C, the DT_{50} is estimated to be significantly <1 day. Transformation products were qualitatively identified as morpholine and formaldehyde.

Therefore under relevant environmental conditions N,N'-Methylenebismorpholine is expected to quickly and completely hydrolyse to formaldehyde and morpholine.

Morpholine is assumed to be stable to hydrolysis under normal field conditions. No experimental data are available to confirm this.

Hydrolysis of **formaldehyde** can be excluded because of the absence of a hydrolysable group in the molecule. However, at room temperature formaldehyde undergoes essentially complete hydration in water forming the formaldehyde hydrate "methylene glycol" ($CH_2(OH)_2$) and its oligomers, namely the low molecular mass poly(oxymethylene)glycols with the following structure $HO(CH_2O)_nH$ (n =8).

Photolysis in water:

Photolytic degradation in water is excluded for **MBM**, as it does not contain any functional group or reactive centre which displays chromophore properties at wavelengths above 290 nm.

As **morpholine** shows no absorption in the UV spectrum (lambda >260 nm), direct photo-chemical degradation in the hydrosphere is unlikely.

Formaldehyde in aqueous solutions forms formaldehyde hydrate, which has no chromophore that is capable of absorbing sunlight and thus photolysis in surface waters is excluded.

Photo-oxidation in air:

Photo-oxidation is excluded for **MBM**, as it does not contain any functional group or reactive centre which displays chromophore properties at wavelengths above 290 nm. The photo-chemical oxidative degradation of MBM was calculated using the computer simulation software AopWin v1.92. An overall OH rate constant of $3.62x10^{-10}$ cm^3/molecule-sec was determined, resulting in an estimated half-life in air of 1.06 hours at 25°C (assuming $5x10^5$ OH/cm^3). Degradation by ozone is expected to be not relevant due to the absence of double bonds. Reaction with NO_3-radicals is estimated to be of minor relevance and to be covered by the reaction with OH-radicals.

As **morpholine** shows no absorption in the UV spectrum (lambda >260 nm), direct photochemical degradation in the atmosphere is unlikely. However morpholine will react with photochemically-produced hydroxyl radicals in the atmosphere. The atmospheric half-life of morpholine resulting from this reaction is estimated to be 2.6h.

In the gas phase, **formaldehyde** is rapidly degraded in air via reaction with OH radicals. The half-life was estimated to be 1.7 days. Degradation by nitrate and ozone is negligible. The decomposition by direct photolysis is 1.5 times higher than by OH radicals. The main transformation products are Hydrogen and Carbon monoxide.

Distribution:

MBM shows very weak adsorption with a K_{oc} value of <17.8 L/kg (ionized, neutral pH). The unionized form is expected at pH >10.5, which is not relevant for the environment.

For **morpholine** a K_{oc} of 8 L/kg was estimated on the basis of its measured log P_{ow} of -0.86. Estimated from its molecular structure the K_{oc} was 5 L/kg.

A K_{oc} of 15.9 L/kg was estimated for **formaldehyde** on the basis of its log P_{ow} of 0.35.

All three substances are therefore expected to be highly mobile in soil.

Accumulation:

MBM

Due to rapid hydrolysis an experimental determination of a BCF value is not possible.

Aquatic compartment:

The calculated logP_{ow} of MBM is -1.53. For substances with a logP_{ow} of 2-6 a BCF_{fish} can be calculated according to TGD (2003). As a worst case approach a logP_{ow} of 1 was used for calculation, which resulted in a BCF_{fish} of 1.41 L/kg for MBM.

Bioaccumulation in aquatic organisms is therefore not expected.

Terrestrial compartment:

Applying the same approach as for the aquatic compartment, a $BCF_{eartworm}$ was calculated with 0.96 L/kg.

Bioaccumulation in terrestrial organisms is therefore not expected.

Morpholine

Aquatic compartment:

An experimentally determined BCF_{fish} for morpholine was <2.8 L/kg, which is in line with the low logP_{ow} of 0.86.

Terrestrial compartment:

There are no data on terrestrial bio-concentration available. However on the basis of the low logP_{ow} of -0.86 and on the estimated K_{OA} of 3.5 terrestrial bioconcentration is not expected.

For substances with a logP_{ow} of 1-8 a $BCF_{earthworm}$ can be calculated according to TGD (2003). As a worst case approach a logP_{ow} of 1 was used for calculation, which resulted in a $BCF_{earthworm}$ of 0.852 L/kg for morpholine.

Formaldehyde

Aquatic compartment:

In experimental studies on bioaccumulation no elevated formaldehyde levels were found. Additional information on log P_{OW} (0.35) as well as the estimated BCF_{fish} (0.396 L/kg) and biomagnification factor for fish-eating predators (1) support the experimental findings that formaldehyde does not bioaccumulate in aquatic biota.

Terrestrial compartment:

The estimated bioaccumulation potential of formaldehyde for terrestrial organisms is low ($BCF_{earthworm}$ = 0.867).

2.2.3.2. Effects assessment

Aquatic compartment (fish, daphnids, algae, micro-organisms):

MBM

The acute toxicity of N,N'-methylenebismorpholine to aquatic organisms was tested in several studies covering all three trophic levels. Due to rapid hydrolysis it was not possible to measure the concentration of MBM in the test media. Therefore the concentration of the hydrolysis product morpholine was analysed in all acute studies. In the chronic daphnia test the concentration of formaldehyde was measured.

Fish:

Based on the nominally confirmed concentration of morpholine (100 mg/L) in a standard laboratory test with (*Oncorhynchus mykiss)* the 96h LC_{50} of MBM was calculated with >107 mg/L.

There are no data available for chronic toxicity of MBM against fish. A justification for non-submission was accepted, since fish appeared to be the least toxic species in the acute toxicity tests.

Invertebrates:

Based on the nominally confirmed concentration of morpholine (24 mg/L) in a 48h standard laboratory test with (*Daphnia magna)* the EC_{50} of OS 157340 (=MBM; purity 98% w/w) was calculated with 26 mg/L.

The chronic toxicity to *Daphnia magna STRAUS* was determined in a 21-day reproduction study and the NOEC of Contram^{TM}ST-1 (=MBM; purity >92%) was calculated with 5 mg/L based on the measured concentration of Formaldehyde of 0.8 mg/L.

Algae:

Algae is the most sensitive species with a calculated E_rC_{50} (0-96h) value of 10 mg OS 157340 (=MBM; purity 98% w/w) based on the nominally confirmed concentration of morpholine of 9.5 mg/L.

The 72h NOE_rC value for MBM was calculated with 2.1 mg/L on the basis of the nominally confirmed concentration of morpholine (2 mg/L).

Micro-organisms:

The 3h NOEC for activated sludge was determined with 32 mg MBM/L (nominal).

Morpholine

To establish the aquatic toxicity of morpholine a data search was conducted in a review (WHO, 1996) and a database (HSDB, 2007), both peer reviewed. For the single studies poor data were presented. Reliable results were identified in a weight of evidence approach.

Fish:

In three studies the 96h LC_{50} of morpholine towards (*Chelon engeli and Oncorhynchus mykiss)* were found to be >100 mg/L. The most reliable 96h LC_{50} value was identified with 180 mg/L (nominally confirmed) using *Oncorhynchus mykiss* as test organism.

There are no chronic toxicity studies available for fish.

Invertebrates:

The 24h EC_{50} values in three studies with *Daphnia magna* were determined with 100 (nom.), 101 (measured) and 119 mg/L (measured). There are no data available for an exposure of 48h. The results confirm each other therefore the 24h EC_{50} value is in the range of 100-119 mg/L. There are no chronic toxicity studies available for daphnia.

Algae:

There are several data available. Algae are again the most sensitive species. The lowest available and most reliable values based on growth rate are the 96h E_rC_{50} of 28 mg/L and the NOE_rC of 10 mg/L. This NOE_rC value is also within the lowest NOECs compared to available NOE_bC values (5- 80 mg/L) of three different species (*Chlorella vulgaris, Selenastrum subspicatus and Selenastrum capricornutum)*.

Micro-organisms:

The most reliable value for respiration inhibition of activated sludge was identified in a standard laboratory test with a 30 min EC_{15} of 1000mg/L.

Formaldehyde

The aquatic toxicity was tested in several studies covering all 3 trophic levels.

Fish:

There are several acute toxicity studies available the lowest reliable acute LC_{50} value is 5.7 mg/L. No reliable chronic toxicity values are available.

Invertebrates:

Two acute toxicity studies are available. The lowest reliable acute EC_{50} value is 5.8 mg/L. There is one chronic toxicity study available with a NOEC of 1.04 mg/L. It has to be considered, that the applicant has not provided a long-term Daphnia study, therefore a new long-term Daphnia study or a letter of access to the already available study needs to be provided by the applicant at product authorisation stage.

Algae:

All acute toxicity values are in the same order of magnitude, with a mean E_rC_{50} value of 5.7 mg/L. There are no chronic data available.

Micro-organisms:

There are two studies available with the lowest EC_{50} of 20.4 mg/L.

Air compartment:

No atmospheric effect studies were available, neither for the parent compound N,N'-methylenebismorpholine nor for the hydrolysis products. Therefore, only a qualitative assessment can be performed.

Due to the low Henry's law constants (c.f. **MBM Doc. III-A 3.2.1, Appendix "Formalde-hyde Core Dossier**" and **Mor Doc. III-A 3.2.1**), the washing out potential and the degra-dation rate constants in air, the atmospheric lifetimes of N,N'-methylenebismorpholine and its hydrolysis products are considered to be too short to have negative effects like global warming potential, stratospheric ozone depletion potential, the potential for tropospheric ozone formation and the acidification potential on the atmosphere. Interaction of N,N'-methylenebismorpholine and its hydrolysis products with relevant atmospheric processes is expected to be negligible.

Terrestrial compartment:

For the terrestrial compartment there are neither toxicity data available for **MBM,** nor for its hydrolysis products **morpholine** and **formaldehyde**. For MBM a justification for non-submission of data was accepted.

PNECs were therefore calculated on the basis of the available PNECs aquatic using the equilibrium partitioning method (TGD, 2003).

2.2.3.3. PBT assessment

MBM

Persistence:

MBM is readily biodegradable with 93% degradation after 28 days based on CO_2 measurements.

P-screening criterion: readily biodegradable => not P

Bioaccumulation:

As a worst case approach a $logP_{ow}$ of 1 (instead of -1.53) was used to calculate a BCF_{fish} of 1.41 L/kg.

B-criterion: BCF: >2000 => not B

Toxicity:

MBM may be considered as local carcinogenic on the basis of read across to formaldehyde, but this conclusion has to be discussed by RAC/COM. No other CMR or endocrine properties with relevance for human health are evident from the data available.

For fish no long term NOEC is available. For daphnia a 21 day NOEC of 5 mg/L and for algae a 72h NOE_rC of 2.1 mg/L are available.

Algae are the most sensitive species in the acute studies. Therefore it can be expected that a chronic NOEC value for fish would not show lower toxicity values than the 72h NOE_rC from algae.

Endocrine disruption

The applicant provided a discussion of potential endocrine effects in terms of potential C and R category 2 effects and QSAR for estrogen-receptor binding concluding that there is no concern for endocrine disruption. N,N'-methylenebismorpholine has not been found on the Endocrine disruptor website of the European Commission4: Annex 13 (List of 146 substances with endocrine disruption categorizations prepared in the Expert meeting) and 15 (List of 66 Category 1 substances with categorisation high, medium or low exposure concern).

T-criterion: in case carcinogenicity will be supported by RAC/COM => T

Conclusion:

According to the available data MBM is not persistent in the environment, it is not bioaccumulative but may be considered as local carcinogenic and consequently toxic.

MBM is neither a vPvB, nor a PBT substance.

Morpholine

Persistence:

Morpholine is readily biodegradable based on DOC measurements with >90% degradation after 28 days.

P-screening criterion: readily biodegradable => not P

Bioaccumulation:

An experimentally determined BCF_{fish} with <2.8 L/kg is available for morpholine.

B-criterion: BCF: >2000 => not B

Toxicity:

The available data do not indicate concern for CMR or endocrine properties.

Chronic NOEC values are not available for fish and daphnia. For algae there is a 96h NOE_rC value of 10 mg/L available. Since algae are by far the most sensitive species in

4 http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list

the acute toxicity tests it is expected that the chronic NOECs from fish and daphnia would not be lower than the 96h NOE_rC value from algae.

Endocrine disruption

The applicant provided a discussion of potential endocrine effects in terms of potential C and R category 2 effects and QSAR for estrogen-receptor binding concluding that there is no concern for endocrine disruption. Morpholine has not been found on the Endocrine disruptor website of the European Commission5: Annex 13 (List of 146 substances with endocrine disruption categorizations prepared in the Expert meeting) and 15 (List of 66 Category 1 substances with categorisation high, medium or low exposure concern).

T-criterion: NOEC <0.01 mg/L => not T

Conclusion:

According to the available data morpholine isn't persistent in the environment, it isn't bioaccumulative and not toxic.

Morpholine is neither a vPvB, nor a PBT substance.

Formaldehyde

Persistence:

Formaldehyde is readily biodegradable fulfilling the 10-d window.

P-screening criterion: readily biodegradable => not P

Bioaccumulation:

A calculated BCF_{fish} with 0.39 L/kg is available for formaldehyde.

B-criterion: BCF: >2000 => not B

Toxicity:

Formaldehyde was classified as local carcinogen category 1B, via the respiratory tract. Other than this no CMR or endocrine properties were evident.

There are no chronic toxicity values available at all for algae and there are no reliable chronic NOEC values available for fish. For daphnia there is a 21d NOEC value available of 1.04 mg/L, based on the age of the first reproduction. Since fish, daphnia and algae show almost identical sensitivity against formaldehyde in the acute studies, it is expected that the chronic NOEC from daphnia is reliable, although chronic NOEC values from fish and algae are not available.

Endocrine disruption

The applicant provided a discussion of potential endocrine effects in terms of potential C and R category 2 effects and QSAR for estrogen-receptor binding concluding that there is

5 http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list

no concern for endocrine disruption. Formaldehyde has not been found on the Endocrine disruptor website of the European Commission6: Annex 13 (List of 146 substances with endocrine disruption categorizations prepared in the Expert meeting) and 15 (List of 66 Category 1 substances with categorisation high, medium or low exposure concern).

T-criterion: due to carcinogenicity => T

Conclusion:

According to the available data formaldehyde doesn't persistent in the environment, it is not bioaccumulative but is considered as local carcinogen and is therefore toxic.

Formaldehyde is neither a vPvB, nor a PBT substance.

Overall conclusion on the vPvB and PBT assessment

MBM as well as its hydrolysis products don't meet the criteria for vPvB nor for PBT substances according to Annex XIII to Regulation (EC) No. 1907/2006. Therefore MBM, formaldehyde and morpholine don't meet the exclusion criteria as listed in Article 5(1)(e) of the BPR. Furthermore MBM and its hydrolysis products don't meet two of the criteria for PBT substances according to Annex XIII to Regulation (EC) No. 1907/2006. Therefore they don't meet the criteria for candidates of substitution as listed in Article 10(1)(d) of the BPR.

As a consequence MBM and its hydrolysis products morpholine and formaldehyde aren't Persistent Organic Pollutants (POP), either.

2.2.3.4. Exposure assessment

General aspects

MBM hydrolyses very rapidly (<<1 day) in the aqueous environment, releasing morpholine and formaldehyde. The parent compound itself is not expected to reach any environmental compartment. Predicted environmental concentrations were therefore only calculated for the hydrolysis products.

PT 6 – In can preservatives

The active substance N,N'-Methylenebismorpholine as manufactured, which is identical to the biocidal product CONTRAM^{TM} ST-1 is intended to be exclusively used as in-can preservative for fuels (PT 6). Although N,N'-Methylenebismorpholine, is produced in Europe, this stage has not been addressed here (agreed at TMI 06). According to the Intended Use (see Doc II-B, chapter 3) the biocidal product containing 100% of N,N'-Methylenebismorpholine is added automatically to fuel, which is expected to happen in a closed system by industrial users at a concentration between 0.01% and 0.1% w/w N,N'-Methylenebismorpholine. Therefore, emissions to the environment will be negligible during this life cycle stage. The only use of the preserved fuel (post-application) is by professionals and non-professionals/general public during the refuel of engines. In the

6 http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list

MOTA v.5 (2012)7 it is stated that for fuels ending up in engines, it is assumed that 100% of the substance will be burnt, thus emissions should not be considered.

Therefore, no exposure assessment was performed for PT 6, since exposure of the parent compound MBM as well as of the hydrolysis products morpholine and formaldehyde to any environmental compartment is not expected during the life cycle stages application and use.

Large storage tanks at the refinery's site may contain vast amounts of water including formaldehyde and morpholine which are eventually be discharged to a STP. Currently no scenario for emission of fuel preservatives from large oil storage tanks along with the aqueous phase exists. However, the volumes discharged to the sewer are expected similar to those of the scenario assessed for PT 13. Therefore, the risk assessment for storage in large tanks is covered by the risk assessment for PT 13.

Therefore no unacceptable risks are expected for any of the environmental compartments at the life cycle stages application, use and for the emissions from storage tanks.

PT 13 – Preservative for metal working fluids

The biocidal product CONTRAMTM ST-1 containing 100% of the active substance N,N'-Methylenebismorpholine (MBM) as manufactured, is intended to be used as preservative for water based emulsifiable metal working fluids (PT 13) by industrial users. According to the Intended Use (see Doc II-B, chapter 3) the ready to use metalworking fluid contains 0.15% w/w N,N'-Methylenebismorpholine/kg metal working fluid.

The estimation of environmental exposure is made by calculating the emissions and then the concentrations for each environmental compartment on the basis of all direct and indirect emissions. The assessments are based on the Emission Scenario Document (EUBEES - ESD) "Harmonisation of Environmental Emission Scenarios for biocides used as metalworking fluid preservatives (product type 13)"[8] and the EUSES Background report (EC 2012)[9] for Tier 1 calculations. For additional calculations (Tier 2) the current report "Gathering of information for the refinement of the Environmental Emission Scenario for metalworking fluids (PT 13) under BPD/R"10 is consulted.

According to the EUBEES - ESD for PT 13 metalworking fluids are used during manufacture and production in the metalworking industry and fall into the categories pure oils and water based fluids. According to the Intended Use N,N'-Methylenebismorpholine is only used in emulsifiable water based metalworking fluids.

7 MOTA - Manual of Technical Agreements of the Biocides Technical Meeting DRAFT V.5, 2012

8 DG ENV/RIVM (Royal Haskoning ENV.C3/SER/2001/0058): "Harmonisation of Environmental Emission Scenarios for biocides used as metalworking fluid preservatives (product type 13)" prepared within the project "Gathering, review and development of environmental emission scenarios for biocides" (EUBEES 2), May 2003

9 EC (2012) European Union System for the Evaluation of Substances 2.1 (EUSES 2.1). Chapter 3, "Model Calculations", commissioned by the European Commission to the National Institute of Public Health and the Environment (RIVM) of The Netherlands. Available via:

http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/euses/euses/

10 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", 27th May 2013

In the EUBEES - ESD for PT 13 only the life cycle stages industrial use, service life and waste treatment are discussed. For metal working fluids the life cycle stages of industrial use and service life are completely interconnected. Emissions to the environment during the production and formulation of metalworking fluids and possible discharges other than those from their intended use and disposal are not considered in the ESD. It assumes that no (relevant) emissions occur during industrial use and it is designed to calculate the environmental release resulting from the waste treatment phase of metalworking fluids. Emissions during the use phase of metalworking fluids are possible, but eventual emissions from industrial use are considered not relevant as compared with emissions from waste treatment plant. Accordingly, relevant emissions to the wastewater only take place during waste treatment and not during industrial use. The Tier 1 calculations assume that all spent metalworking fluid as well as cleaning water and mixing containers or work pieces are disposed of as waste to an external treatment plant as stated in the EUBEES - ESD for PT 13. Hence, the Tier 2 calculations based on the Fraunhofer report consider an external waste treatment as well in addition to suggestions for refinement made in the above cited paper from the Fraunhofer Institute.

2.2.3.5. Risk characterisation

General aspects

MBM hydrolyses very rapidly (<<1 day) in the aqueous environment, releasing morpholine and formaldehyde. The parent compound itself is therefore not expected to reach any environmental compartment. It is therefore exclusively the hydrolysis products, which are considered in the risk characterisation.

PT 6 – In can preservatives

In PT 6 the biocidal product CONTRAM™ ST-1, is intended to be exclusively used as in-can preservative for fuel. According to the Intended Use (see Doc II-B, chapter 3) the product is added automatically to fuels by industrial users at concentrations between 0.01 and 0.1% w/w MBM (corresponding to a maximum concentration of 0.085% w/w morpholine and 0.015% w/w formaldehyde). The preserved fuel is used by professionals and non-professionals/general public during the refuel of engines.

In MOTA v.5 (2012)11 it is stated that “For fuel ending up in an engine, it is assumed that 100% of the substance will be burnt, thus emissions should not be considered”. Therefore predicted environmental concentrations were not calculated for PT 6 (see Doc II-B, chapter 5.1).

As a consequence no risk characterisation was performed for PT 6, since exposure of the parent compound MBM as well as of the hydrolysis products morpholine and formaldehyde to any environmental compartment is not expected during the life cycle stages application and use.

Storage Scenario

Large storage tanks at the refinery’s site may contain vast amounts of water which are discharged separately. Considering that the compound is miscible in all proportions with water and hydrolyses rather fast the active substance will not accumulate in the oil phase, but will be discharged together with the waste water. Discharge to the STP is likely, but due to the presence of hydrocarbons in the aqueous phase (the so-called water-accommodated fraction) waste water must be treated according to environmental

11 MOTA - Manual of Technical Agreements of the Biocides Technical Meeting DRAFT V.5, 2012

legislations. However, the aqueous phase is eventually discharged to the sewer after waste water treatment.

A scenario for emission of fuel preservatives from large oil storage tanks along with the aqueous phase does not exist currently. The applicant provided some information concerning waste water volumes from refineries and storage sites. Considering that PT13 was assessed for the hydrolysis products formaldehyde and morpholine as well for which the volumes discharged to the sewer are expected similar to that of large storage tanks, the later may cover the risk assessment for fuel preservatives as well.

PT 13 – Preservative for metal working fluids

The biocidal product CONTRAM™ ST-1 is intended to be used as preservative for water based emulsifiable metalworking fluids (PT 13). According to the Intended Use the ready to use metalworking fluid contains 0.15% w/w MBM/kg (corresponding to 0.0225% w/w Formaldehyde and 0.1275% w/w morpholine). This concentration can be achieved either by direct application of the biocide, containing 100% MBM, to the metal working fluid or by adding a lubricant concentrate of approximately 3% of the biocide. Exposure calculations were performed for direct application of the (100%) biocide, which also covers the lubricant concentrate use.

In the EUBEES ESD for PT 13 it is assumed that relevant emission to wastewater only takes place during the waste treatment stage, which will lead to direct releases to STP. In this report release of the waste water to an external waste water treatment plant is assumed.

Tier 1 PEC calculations (according to EUBEES - ESD for PT 13, 2003)12 and the **Tier 2** PEC calculations according to suggestions of the Fraunhofer Institute, 201313 were performed for all relevant compartments (see Doc II-B, chapter 5.2).

At the BPC Working Group in June 2014 it was agreed that even if there was an unacceptable risk this needs to be revised at product authorisation level in the light of the new guidance for PT 13 currently under preparation. The reason for this statement is a harmonised approach between the different dossiers for PT 13.

Atmosphere

No atmospheric effect studies are available, neither for the parent compound N,N'-methylenebismorpholine nor for the hydrolysis products. Therefore, only a qualitative assessment can be performed. The TNsG on data requirements recommends a qualitative discussion of potential breakdown products, as well as an assessment of the global warming potential, stratospheric ozone depletion potential, the potential for tropospheric ozone formation and the acidification potential. Regarding the fast hydrolysis of N,N'-methylenebismorpholine, it is not expected to remain in the environment for a long time. The impact of this substance on the environment is expected to be determined mainly by its hydrolysis products.

12 DG ENV/RIVM (Royal Haskoning ENV.C3/SER/2001/0058): "Harmonisation of Environmental Emission Scenarios for biocides used as metalworking fluid preservatives (product type 13)" prepared within the project "Gathering, review and development of environmental emission scenarios for biocides" (EUBEES 2) May 2003

13 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", 27th May 2013

Due to the low Henry's law constants (c.f. **MBM Doc. III-A 3.2.1, Appendix "Formaldehyde Core Dossier"** and **Mor Doc. III-A 3.2.1**), the washing out potential and the degradation rate constants in air, the atmospheric lifetimes of N,N'-methylenebismorpholine and its hydrolysis products are considered to be too short to have negative effects like global warming potential, stratospheric ozone depletion potential, the potential for tropospheric ozone formation and the acidification potential on the atmosphere. Therefore, the interaction of N,N'-methylenebismorpholine and its hydrolysis products with relevant atmospheric processes is expected to be negligible.

Aquatic compartment

STP:

Usually used metal working fluid is collected and treated in a special facility predominantly treating industrial waste water. (see Doc. II-B, chapter 5.2.2.2 PEC in STP).

The $PNEC_{STP}$ for morpholine was calculated with 10 mg/L.

The PNEC $_{STP}$ for formaldehyde was calculated with 0.2 mg/L (see Doc. II-A, chapter 4.2.5 and 4.2.6 PNEC calculations and Overview).

Table 2.2.3.5-1: Tier 1 and 2 PEC/PNEC ratios for morpholine in STP resulting from direct dosing

Exposure scenario	**PEC_{STP} (mg/L)**	**PEC/PNEC**
	$PNEC_{STP}$: 10 mg/L	
Tier 1 (EUBEES Approach)		
Waste treatment	16	**1.6**
Tier 2 (Fraunhofer Report Approach)		
Waste treatment	0.80	**8.00×10^{-2}**

Table 2.2.3.5-2 Tier 1 and 2 PEC/PNEC ratios for formaldehyde in STP resulting from direct dosing

Exposure scenario	**PEC_{STP} (mg/L)**	**PEC/PNEC**
	$PNEC_{STP}$: 0.2 mg/L	
Tier 1 (EUBEES Approach)		
Waste treatment	2.56	**12.80**
Tier 2 (Fraunhofer Report Approach)		
Waste treatment	0.128	**0.64**

Conclusion:

Tier 1 PEC/PNEC values for morpholine as well as for formaldehyde are >1, indicating a risk to micro-organisms in STP from both metabolites. It has to be kept in mind, that a worst case scenario was calculated, assuming that the metalworking fluid still contains 0.15% w/w of MBM (corresponding to 0.0225% w/w formaldehyde and 0.1275% w/w morpholine) at the end of service life and that the whole amount of treated volume is released to an STP in one single event.

Tier 2 calculations based on the Fraunhofer Report were performed, considering a dilution factor of 100 for dilution from the company to an STP, a dilution factor of 100 for dilution from STP to a river and a factor of relevance of 0.5. The resulting PEC/PNEC ratios are <1 for morpholine and formaldehyde, indicating an acceptable risk.

Surface water:

According to the Intended Use (Doc. II-B, chapter 3), only indirect exposure via STP is possible for surface water, assuming that the effluent of the sewage treatment plant is diluted into surface water (see Doc. II-B, chapter 5.2.2.3 PEC in surface water).

The $PNEC_{water}$ for morpholine was calculated with 0.028 mg/L.

The $PNEC_{water}$ for formaldehyde was calculated with 0.0104 mg/L (see Doc. II-A, chapter 4.2.5 and 4.2.6 PNEC calculations and Overview).

Table 2.2.3.5-3: Tier 1 and 2 PEC/PNEC ratios for morpholine in the aquatic compartment resulting from direct dosing

Exposure scenario	**PEC local (mg/L)**	**PEC/PNEC**
	$PNEC_{water}$: 0.028 mg/L	
Tier 1 (EUBEES Approach)		
Local PEC in surface water during emission episode (dissolved)	1.6	**57.14**
Tier 2 (Fraunhofer Report Approach)		
Local PEC in surface water during emission episode (dissolved)	8.00×10^{-3}	**0.29**

Table 2.2.3.5-4: Tier 1 and 2 PEC/PNEC ratios for formaldehyde in the aquatic compartment

Exposure scenario	**PEC local (mg/L)**	**PEC/PNEC**
	$PNEC_{surface\ water}$: 0.0104 mg/L	
Tier 1 (EUBEES Approach)		
Local PEC in surface water during emission episode (dissolved)	0.256	**24.62**
Tier 2 (Fraunhofer Report Approach)		
Local PEC in surface water during emission episode (dissolved)	1.28×10^{-3}	**0.12**

Conclusion

Tier 1 PEC/PNEC ratios for morpholine as well as for formaldehyde are >1, indicating a risk to aquatic organisms from both metabolites. It has to be kept in mind that the ESD for PT 13 is very conservative and that degradation processes were ignored in the calculations.

Tier 2 calculations based on the Fraunhofer Report were performed, considering a dilution factor of 100 for dilution from STP to the river and a factor of relevance of 0.5. The resulting PEC/PNEC ratios are <1 for morpholine and formaldehyde, indicating an acceptable risk.

Surface water used for drinking water

The concentrations for morpholine and formaldehyde in surface water exceed the parametric value of 0.1 µg/L, according to drinking water Directive 98/83/EC, in all calculated scenarios (see Table 2.3.2.2-1 and Table 2.3.2.2-2).

Regulation EU (No) 528/2012, Annex VI, article 69 states that surface water in or from the area of envisaged use intended for the abstraction of drinking water should not exceed the value for organic pesticides of 0.1 µg/L fixed by Directive 98/83/EC.

On the other hand the $PEC_{surface\ water}$ doesn't necessarily correspond with the PEC for the concentration at the water abstraction point. The calculations do not take into account the rapid degradation of formaldehyde in water, dilution in surface water and the "background concentration" of the compounds. At present there are no tools available to calculate such a PEC, taking into account these processes that may occur during the water flow from the STP to the water abstraction point.

Therefore the release of biocides used as disinfectant for metalworking fluids line and metalworking fluids has to be considered by the relevant national authorities when issuing permits for recovery plants (according to an agreement at Technical Meeting IV09).

Sediment assessment and persistence:

According to TGD, Part II (EC 2003) in general, substances with a K_{oc} <500 L/kg are not likely to sorb to sediment. The K_{oc} values of morpholine and formaldehyde are 8 L/kg and 15.9 L/kg, respectively. Therefore, no risk assessment for the sediment compartment was performed.

Morpholine degraded readily in separate studies according to OECD 301E (>90% in 28 days) based on DOC removal.

Formaldehyde is expected to be readily biodegradable, fulfilling the 10d window on the basis of a study according to OECD 301A.

For morpholine and formaldehyde there are no DT_{50} values available from laboratory water/sediment degradation studies.

On the basis of the ready biodegradability and the low K_{oc} values of morpholine and formaldehyde formation of non-extractable residues is not expected in laboratory tests in amounts exceeding 70% of the initial dose.

Conclusion

Morpholine and formaldehyde are not persistent in sediment.

Terrestrial compartment

Terrestrial organisms:

According to the intended use only indirect exposure of agricultural soils through fertilization with sludge from a STP is considered relevant.

The PECs were calculated according to TGD, part II (EC 2003) for arable soil and grassland as the average concentrations over certain time-periods (see Doc. II-B, chapter 5.2.2.5 PEC in soil).

The PNECs for soil organisms were calculated according to the equilibrium partitioning method on the basis of the $PNEC_{water}$.

The $PNEC_{soil}$ for morpholine was calculated with 0.012 mg/kg_{wwt}.

The $PNEC_{soil}$ for formaldehyde was calculated with 0.00416 $mg/kg_{wwt.}$ (see Doc. II-A, chapter 4.2.5 and 4.2.6 PNEC calculations and Overview).

Table 2.2.3.5-5: Tier 1 and 2 PEC/PNEC ratios for morpholine in the terrestrial compartment resulting from direct dosing

Exposure scenario	**PEC local (mg/kg_{wwt})**	**PEC/PNEC**
	$PNEC_{soil}$: 0.012 mg/kg_{wwt}	
Tier 1 (EUBEES Approach)		
Local PEC in agric. soil (total) averaged over 30 days	0.0987	8.23
Local PEC in agric. soil (total) averaged over 180 days	0.024	2.00
Local PEC in grassland (total) averaged over 180 days	6.87×10^{-3}	0.57
Tier 2 (Fraunhofer Report Approach)		
Local PEC in agric. soil (total) averaged over 30 days	4.93×10^{-3}	0.41
Local PEC in agric. soil (total) averaged over 180 days	1.20×10^{-3}	0.10
Local PEC in grassland (total) averaged over 180 days	3.43×10^{-4}	0.03

Table 2.2.3.5-6: Tier 1 and 2 PEC/PNEC ratios for formaldehyde in the terrestrial compartment resulting from direct dosing

Exposure scenario	**PEC local (mg/kg_{wwt})**	**PEC/PNEC**
	$PNEC_{soil}$: 0.00416 mg/kg_{wwt}	
Tier 1 (EUBEES Approach)		
Local PEC in agric. soil (total) averaged over 30 days	0.0753	18.10
Local PEC in agric. soil (total) averaged over 180 days	0.0214	5.14
Local PEC in grassland (total) averaged over 180 days	7.09×10^{-3}	1.70
Tier 2 (Fraunhofer Report Approach)		
Local PEC in agric. soil (total) averaged over 30 days	3.76×10^{-3}	0.90
Local PEC in agric. soil (total) averaged over 180 days	1.07×10^{-3}	0.26
Local PEC in grassland (total) averaged over 180 days	3.54×10^{-4}	0.09

Conclusion

Tier 1 PEC/PNEC values for morpholine as well as for formaldehyde are >1, with the exception of the scenario for grassland (180 days) for morpholine, indicating a risk to soil organisms from both metabolites.

Tier 2 was calculated based on the Fraunhofer Report, which resulted in PEC/PNEC ratios <1 for both metabolites, indicating an acceptable risk to soil organisms.

Persistence in soil:

Morpholine degraded readily in separate studies according to OECD 301E (>90% in 28 days) based on DOC removal.

Formaldehyde is expected to be readily biodegradable, fulfilling the 10d window on the basis of a study according to OECD 301A.

For morpholine and formaldehyde there are no DT_{50} values available from soil field degradation studies.

On the basis of the ready biodegradability and the low K_{oc} values of morpholine and formaldehyde formation of non-extractable residues is not expected in laboratory tests in amounts exceeding 70% of the initial dose.

Conclusion

Morpholine and formaldehyde are not persistent in soil.

Groundwater:

According to the TDG, part II (EC 2003) the concentration in pore water of soil is taken as an indication for potential groundwater levels.

A **Tier 1** (based on the EUBEES – ESD) calculation of the predicted environmental concen-trations of morpholine and formaldehyde in groundwater under agricultural soil after contin-uous sludge application over 10 years gives values of 131µg/L and 53.6 µg/L, respectively (see Doc. II-B, section 5.2.2.6).

Based on **Tier 2** (based on the Fraunhofer report) calculations the concentrations of morpholine and formaldehyde in groundwater under agricultural soil after continuous sludge application over 10 years are 6.54 µg/L and 2.68 µg/L, respectively for the active substance. These values are still above the parametric value of 0.1µg/L.

Therefore, potential groundwater concentrations for both hydrolysis products were calculated using FOCUS Pearl v. 4.4.4. groundwater model.

The calculated groundwater concentrations for morpholine under arable soil show in all nine scenarios values exceeding the threshold value of 0.1 µg/L for winter cereals and in three scenarios (Jokioinen not applicable) for maize. The concentrations under grassland are all <0.1 µg/L (see Doc. II-B, table 5.2.6-4 and 5.2.6-5).

The calculated groundwater concentrations for formaldehyde under arable soil (maize) and under grassland result in groundwater concentrations <0.1µg/L. The concentrations under arable soil with winter cereals result in six scenarios exceed the threshold value of 0.1 µg/L (see Doc. II-B, table 5.2.6-4 and 5.2.6-5).

Conclusion

As agreed in TMII 12, five scenarios for each application setting that show no risk, are necessary for annex I inclusion. However, it is still under discussion which one of the two plant species (winter cereals or maize) should be used for the calculation of groundwater concentrations under arable soil. Therefore, if winter cereals are used the requirement of five scenarios indicating no risk is not achieved for morpholine and formaldehyde. However, if maize is used then the requirement of five scenarios indicating no risk is achieved for all application settings.

Depending on the crop species morpholine and formaldehyde are or are not likely to have unacceptable effects on groundwater according to Directives 98/83/EC and 2006/118/EC.

Furthermore, at the BPC Working Group in June 2014 it was agreed that even if there is an unacceptable risk this needs to be revised at product authorisation level in the light of the new guidance for PT 13 currently under preparation. The reason for this statement is a harmonised approach between the different dossiers for PT 13.

Persistence in soil:

Morpholine degraded readily in separate studies according to OECD 301E (>90% in 28 days) based on DOC removal.

Formaldehyde is expected to be readily biodegradable, fulfilling the 10d window on the basis of a study according to OECD 301A.

For morpholine and formaldehyde there are no DT_{50} values available from soil field degradation studies.

On the basis of the ready biodegradability and the low K_{oc} values of morpholine and formaldehyde formation of non-extractable residues is not expected in laboratory tests in amounts exceeding 70% of the initial dose.

Conclusion

Morpholine and formaldehyde are not persistent in soil.

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

According to the TGD on Risk Assessment, part II (EC 2003), concern for a bioaccumulation potential of a substance only exists if a substance has a log K_{OW} >3, is highly adsorptive (or belongs to a structural class of substances that is known to bioaccumulate) and no mitigations regarding its degradation properties exist.

None of these points apply to morpholine and formaldehyde. This is supported by an experimental BCF_{fish} for morpholine of <2.8 L/kg and estimated BCF aquatic and terrestrial values for formaldehyde of 0.396 L/kg and 0.867 L/kg, respectively. Additionally in most cases hydrolysis products are more hydrophilic than the parent compound and as a consequence will have lower potential for bioaccumulation.

There is no indication of a bioaccumulation potential for morpholine and formaldehyde and therefore no risk assessment for secondary poisoning was performed.

2.2.4. List of endpoints

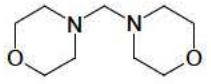
In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

APPENDIX I: LIST OF ENDPOINTS

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

Active substance	N,N'-Methylenebismorpholine (short: MBM)
Product-type	6, 13

Identity

Chemical name (IUPAC)	4-(morpholin-4-ylmethyl)morpholine
Chemical name (CA)	N,N'-Methylenebismorpholine, 4,4'-Methylenedimorpholine Dimorpholinomethane
CAS No	5625-90-1
EC No	227-062-3
Other substance No.	n.a.
Minimum purity of the active substance as manufactured (g/kg or g/l)	921 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	There are no constituents in the substance which are classified as „toxic", „highly toxic" or „dangerous for the environment".
Molecular formula	$C_9H_{18}N_2O_2$
Molecular mass	186.26 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	MBM: 18 - 21 °C (purity: 98%w/w) Morpholine: range -3,1 to -5°C
Boiling point (state purity)	MBM :266.4°C (purity: 98%w/w) Morpholine: 128°C
Temperature of decomposition	-
Appearance (state purity)	MBM: Liquid; Extremely pale yellow; Slightly amine like Morpholine: oily ,hygroscopic, colourless liquid
Relative density (state purity)	MBM: relative density: 1.05 (20.0°C, purity: 98%w/w) Density: 1.0647 g/cm3 (20°C, purity: min.92.1%w/w) Morpholine: relative density: 1.0001 (20°C)

Surface tension	Not applicable due to hydrolysis in aqueous solution
Vapour pressure (in Pa, state temperature)	MBM: 0.625 Pa (25°C calculated with Epi Suite 3.12); 0.443 Pa (20°C calculated with EUSES) Morpholine: 1.1 kPa (20°C); 3.2 kPa (40°C); 1.34 kPa (25°C)
Henry's law constant (Pa m^3 mol^{-1})	MBM: Calculated: $2.72x10^{-5}$ Pa m^3 $mole^{-1}$ Morpholin: 49 Pa m^3 mol^{-1}(20°C); 244 Pa*m^3*mol^{-1} and 0.012 Pa*m^3*mol^{-1}(25°C)
Solubility in water (g/l or mg/l, state temperature)	Test substance hydrolyses; miscible in all proportions; temperature: 10.0 – 30.0°C; pH: 5 – 9 Morpholine: miscible with water ; low soluble in alkaline aqueous solutions
Solubility in organic solvents (in g/l or mg/l, state temperature)	MBM: Solubility in n-heptane: 2000 – 2500 mg/L (20.5°C) Result completely miscible in DMSO, Toluene, Ethanol, n-octanol, Acetone; Partially soluble in Cyclohexane (Concentrations tested: 5000, 2500, 1000, and 500 mg/mL at 21-23 °C) Morpholine: miscible with, for instance, methanol, ethanol, acetone, diethyl ether, benzene, toluene, xylol.
Stability in organic solvents used in biocidal products including relevant breakdown products	MBM: The substance and the biocidal products are solely handled and marketed as aqueous solution which contains no organic solvents. Morpholine: Not relevant for hydrolysis product
Partition coefficient (log P_{OW}) (state temperature)	MBM. log Pow = < 0.3 (hydrolysed test substance) ; pH : 5, 7, 9 at 30°C; Calculation: log Pow = -1.53 (EpiSuite) Morpholine: -0.86 (pH no data), and -2.55 (pH 7)
Dissociation constant	MBM: pH = 10.48 at 20°C (1% CONTRAM™ ST-1 in dist. Water) Morpholine pKa: 8.5 (25°C) and 8.33 (25°C)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	MBM: There are no absorption maxima above 290 nm.
Flammability	MBM: Flash point: 115°C Melting point is below 100°C. Therefore, determination of flashpoint is sufficient for the test substance. Morpholine Flash point: open cup: 38°C; closed cup: 35,31°C Morpholine is a flammable liquid Category 3.
Explosive properties	MBM: There is no structural alert for explosive

properties. Morpholine: Explosion limits in air: 1.4-13.1 vol%; 1.8-11 vol%; 1.8-15.2 vol%

Classification and proposed labelling

with regard to physical/chemical data	-
with regard to toxicological data	1st proposal by RMS: Skin Corr. 1: H314: Causes severe skin burns and eye damage Skin Sens. 1: H317: May cause an allergic skin reaction Carc. 1B: H350: May cause cancer Muta 2: H341: Suspected of causing genetic defects 2nd proposal by applicant: Skin Corr. 1: H314: Causes severe skin burns and eye damage
with regard to data on ecotoxicology and on fate and behaviour	For environmental hazards no classification and labelling according to Regulation (EC) No 1272/2008 is needed, since neither the active substance (MBM), nor the hydrolysis products (Formaldehyde and Morpholine) fulfil the classification and labelling criteria.

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	^{1}H- and ^{13}C-NMR method
Impurities in technical active substance (principle of method)	[redacted]

Analytical methods for residues

Soil (principle of method and LOQ)	MBM: Not applicable Morpholine: Not applicable
Air (principle of method and LOQ)	MBM: Not applicable Morpholine: enrichement on XAD-7, GC-FID measurement after extraction. LOQ = 160 µg/m³
Water (principle of method and LOQ)	MBM: Not applicable Morpholine: GC analysis using borosilicate glass column (silylated) and graphitized carbon coated with polyethylene glycol. LOQ = 1 mg/L
Body fluids and tissues (principle of method and LOQ)	MBM: Not applicable Morpholine: Headspace-GC/MS. LOQ_{blood} = 1 µg/ml blood LOQ_{urine} = 10 µg/ml urine GC/FID LOQ_{plasma} = 5 µg/ml plasma LOQ_{tissue} = 25 µg/g tissue LOQ_{urine} = 125 µg/ml urine
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	MBM: Not applicable Morpholine: Not applicable
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	MBM: Not applicable Morpholine: Not applicable

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	No data, assumption 100%
Rate and extent of dermal absorption:	MBM (0.15%): 60% MBM (3%): 70% applied as 10 µL/cm2 for 8 hours
Rate and extent of inhalative absorption:	after intratracheal instillation rapidly absorbed, assumption 100%
Distribution:	assumption of hydrolysis to formaldehyde and morpholine at the site of contact with biological tissue, reactivity of formaldehyde with biological tissue Data on products of hydrolysis Formaldehyde: reactivity at the site of 1st contact Morpholine: bio-available but rapidly excreted
Potential for accumulation:	No data, not expected
Rate and extent of excretion:	radioactivity from the morpholine-labelled MBM after intratracheal instillation rapid excretion via urine after intratracheal instillation of methylene-labelled MBM about 60% of radioactivity were expired into air further data on products of hydrolysis: Formaldehyde: exhaled CO_2, formate via urine (rapid) Morpholine: excreted unchanged via urine (rapid)
Toxicologically significant metabolite(s)	MBM hydrolysis to formaldehyde and morpholine

Acute toxicity

Rat LD_{50} oral	500 < LD50 < 2000 mg/kg bw
Rat LD_{50} dermal	No data, corrosive
Rat LC_{50} inhalation	No data, corrosive
Skin irritation	corrosive
Eye irritation	corrosive
Skin sensitization (test method used and result)	Guinea pig maximization test, inconclusive. WoE evaluation: skin sensitizer due to formaldehyde release at site of contact with human tissue

Repeated dose toxicity

Species/ target / critical effect	a) Rat (oral)/local effects (stomach) b) Rabbit (oral)/ local effects (stomach)
Lowest relevant oral NOAEC / LOAEC	NOAEC 0.75 (a) and 1% (b) LOAEC 2.5% (a) and 3% (b)
Lowest relevant oral NOAEL / LOEL	a) no systemic effects up to the highest dose tested: NOAEL ≥ 150 mg/kg bw day b) systemic effects at highest dose tested in terms of reduced food consumption and body weight gain considered secondary to local stomach effects: LOEL = 100 mg/kg bw day (10% in corn oil)
Lowest relevant dermal NOAEL / LOAEL	No data, corrosive
Lowest relevant inhalation NOAEL / LOAEL	No data, corrosive

Genotoxicity

In-vitro: Salmonella microsome assay: weak positive Chromosome aberration test in CHO cells: positive Mouse lymphoma assay: positive In-vivo: Mouse bone marrow micronucleus assay: negative Unscheduled DNA synthesis in rats: negative

Carcinogenicity

Species/type of tumour	No data available but implementation of a long-term study scientifically unjustified; carcinogenic effects of formaldehyde sufficiently documented

Reproductive toxicity

Species/ Reproduction target / critical effect	Rat (subchronic, oral)/ reproductive organs/ no effects
Lowest relevant reproductive NOAEL / LOAEL	150 mg/kg bw/day / > 150 mg/kg bw/day
Species/Developmental target / critical effect	Rabbit / developmental toxicity / no effects
Lowest relevant developmental NOAEL / LOAEL	100 mg/kg bw/day / >100 mg/kg bw/day

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Rat, subchronic, oral / no neurotoxic effects
Lowest relevant developmental NOAEL / LOAEL.	NOAEL > 150 mg/kg bw/day

Other toxicological studies

....	No data available

Medical data

....	Medical surveillance at workplace No other medical data on active substance available

Summary	Value	Study	Safety factor
MBM systemic AEL, short, medium and long term	0.75 mg/kg bw day	Rat oral subchronic study	200 = 10x10 (for intra- and interspecies uncertainty) x 2 (for extrapolation subchronic to chronic)
Formaldehyde systemic AEL, short, medium and long term	0.15 mg/kg bw day	Rat, overall (28-d, 90-d, 2-yr)	100 = 10x10 (for intra- and interspecies uncertainty)
MBM local respiratory AEC short, medium and long term	0.75 µg/L	Molar read across from formaldehyde, factor 6.2.	
Formaldehyde local respiratory AEC short, medium and long term	0.12 µg/L	Human, eye irritation	3
		Human, overall ocular/respiratory irritation	114

14 population based NOAEC, no additional safety factor for intraspecies variability required

	Rat, Monkey, 6-mo	1015

Acceptable exposure scenarios (including method of calculation)

Production of active substance (user:)	Not assessed
Formulation of biocidal product (user:)	Not assessed
Application of biocidal product (user:)	PT 6: Use for fuels Formulation of fuels (worker): inhalation and dermal exposures* Refueling of engines (general public, professional): inhalation and dermal exposures* PT 13: Use for metalworking fluids Formulation of lubricant concentrate (worker): inhalation and dermal exposures* Use in metal working processes (worker, professional) inhalation and dermal exposures* *inhalation: RMM are considered to be efficient enough that concentrations in air do not exceed AEC of formaldehyde or MBM
Indirect exposure as a result of use	PT 6: General public (bystanders) during refuelling of engines PT 13: Not expected
Exposure of pets	PT 6, 13: Not expected
Dietary Exposure	PT 6, 13: Not expected

15 Default safety factor for interspecies variability reduced from 10 to 1, remaining default safety factor for intraspecies variability of 10 may be reduced to 5 (BfR, 2006; without relevance for AEC).

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)	pH 5: **DT_{50} < 2.4 h at 50°** **conclusion / estimate: DT_{50} < 1 day at 25°C**
	pH 7: **DT_{50}< 2.4 h at 50°C** **conclusion / estimate: DT_{50} < 1 day at 25°C**
	pH 9: **DT_{50}< 2.4 h at 50°C** **conclusion / estimate: DT_{50} < 1 day at 25°C**
	Metabolites: formaldehyde (CAS: 50-00-0) morpholine(CAS: 110-91-8)
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	No study available. This degradation pathway is considered to be of minor relevance, as the UV spectrum indicates no absorption of light at wave-lengths >290 nm.
Readily biodegradable (yes/no)	MBM: Yes; (93% degradation based on CO_2 measurements after 28days, CO_2 Evolution test) Morpholine: Yes; (>90% degradation based on DOC measurements after 28 days, Modified OECD screening test)
Biodegradation in seawater	-
Non-extractable residues	-
Distribution in water / sediment systems (active substance)	-
Distribution in water / sediment systems (metabolites)	-

Route and rate of degradation in soil

Mineralization (aerobic)	-
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (20°C, aerobic): -
	DT_{90lab} (20°C, aerobic):-
	DT_{50lab} (10°C, aerobic):-
	DT_{50lab} (20°C, anaerobic):-
	degradation in the saturated zone:-
Field studies (state location, range or	DT_{50f}:-

median with number of measurements)	
	DT_{90f}:-
Anaerobic degradation	
Soil photolysis	
Non-extractable residues	-
Relevant metabolites - name and/or code, % of applied active ingredient (range and maximum)	-
Soil accumulation and plateau concentration	-

Adsorption / desorption

Ka , Kd	
Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	MBM: K_{oc} <17.8 L/kg (ionized form; neutral pH; measured) Unionized form is expected at pH >10.5, which is not relevant for the environment. Morpholine: K_{oc} =8 L/kg (estimated on basis of its measured log P_{ow} of -0.86.

Fate and behaviour in air

Direct photolysis in air	No study available. This degradation pathway is considered to be of minor relevance, as the UV spectrum indicates no absorption of light at wave-lengths >290 nm.
Quantum yield of direct photolysis	---
Photo-oxidative degradation in air	AOPWIN v1.91 Prediction Overall OH rate constant = $3.62x10^{-10}$ cm^3/molecule·sec DT50 calculated = 1.06 hours ($5x10^5$ OH/cm)
Volatilization	Regarding calculated Henry's law constantof $2.72 \cdot 10^{-5}$ Pa m^3 $mole^{-1}$, volatility of substance from aqueous solution is considered to be low.

Monitoring data, if available

Soil (indicate location and type of study)	-
Surface water (indicate location and type of study)	-

Ground water (indicate location and type of study)	-
Air (indicate location and type of study)	-

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity (mg/L)
Fish – Test substance: MBM			
Oncorhynchus mykiss	9h, semi-static	Mortality, LC_{50}	107 mg/L calc. based on measured Morpholine
Fish – Test substance: Morpholine			
Chelon engeli	96h, static	Mortality, TLm	100-180 mg/L (supportive data)
Oncorhynchus mykiss	96h, static, hard water	Mortality, LC_{50}	380 mg/L (supportive data)
Oncorhynchus mykiss	96h, static, soft water	Mortality, LC_{50}	180 mg/L (supportive data, most reliable)
Invertebrates - Test substance: MBM			
Daphnia magna	48h, static	Mobility, EC_{50}	26 mg/L calc. based on measured Morpholine
Daphnia magna STRAUS (clone 5)	21 days	Cumulative offspring of survivors, NOEC	5 mg/L
Invertebrates - Test substance: Morpholine			
Daphnia magna	24h, static	Mobility, EC_{50}	119 mg/L (supportive data)
Daphnia magna	24h, static	Mobility, EC_{50}	101 mg/L (supportive data)
Daphnia magna	24h, static	Mobility, EC_{50}	100 mg/L (supportive data,)
Algae - Test substance: MBM			
Pseudokirchneriella subcapitata	96h, static	Growth rate, E_rC_{50}	10 mg/L calc. based on measured Morpholine

Pseudokirchneriella subcapitata	72h, static	Growth rate, NOE_rC	2 mg/L calc. based on measured Morpholine
Algae - Test substance: Morpholine			
Selenastrum capricornutum	96h, static	Growth rate, E_rC_{50}	28 mg/L (supportive data, most reliable)
Selenastrum capricornutum	96h, static	Growth rate, NOE_rC	10 mg/L (supportive data, most reliable)
Chlorella vulgaris	24-120h	Growth rate, E_bC_0	80 mg/L (supportive data)
Selenastrum subspicatus	24-120h	Growth rate, E_bC_0	5 mg/L (supportive data)
Selenastrum capricornutum	24-120h	Growth rate, E_bC_0	50 mg/L (supportive data)
Microorganisms - Test substance: MBM			
Activated sludge	3h, static	Inhibition of respira-tion, NOEC	32 mg/L (nominal)
Microorganisms - Test substance: Morpholine			
Activated sludge	30 min	Inhibition of respira-tion, EC_{20}	1000 mg/L (nominal) (supportive data, most reliable)
Pseudomonas (4 strains)		Growth rate, NOE_rC	8700 mg/L (supportive data)
Pseudomonas putida	16h	TT	310 mg/L (supportive data)
Microcystis aeruginosa	192h	TT	1.7 mg/L (supportive data)

Effects on earthworms or other soil non-target organisms

Acute toxicity to ……..	No data available
Reproductive toxicity to ……	No data available

Effects on soil micro-organisms

Nitrogen mineralization	No data available

Carbon mineralization	No data available

Effects on terrestrial vertebrates

Acute toxicity to mammals	No data available
Acute toxicity to birds	No data available
Dietary toxicity to birds	No data available
Reproductive toxicity to birds	No data available

Effects on honeybees

Acute oral toxicity	No data available
Acute contact toxicity	No data available

Effects on other beneficial arthropods

Acute oral toxicity	No data available
Acute contact toxicity	No data available
Acute toxicity to ……..	No data available

Bioconcentration

Bioconcentration factor aquatic MBM (BCF_{fish})	BCF_{fish} = 1.41 L/kg (calculated as a worst case approach for a log Pow of 1 with QSAR (TGD, Veith et al. 1979)); Log Pow = -1.53(calculated)
Bioconcentration factor aquatic Morpholine (BCF_{fish})	BCF_{fish} < 2.8 L/kg (measured) Log Pow = -0.86 (measured)
Bioconcentration factor terrestric MBM ($BCF_{earthworm}$)	$BCF_{earthworm}$ = 0.96 L/kg (calculated as a worst case approach for a log Pow of 1 with QSAR (TGD, Veith et al. 1979)); Log Pow = -1.53 (calculated)
Bioconcentration factor terrestric Morpholine ($BCF_{earthworm}$)	Bioconcentration is not expected (Log Pow of -0.86 (measured), K_{OA} of <5)
Depration time (DT_{50}) (DT_{90})	-
Level of metabolites (%) in organisms accounting for > 10 % of residues	-

Chapter 6: Other End Points

APPENDIX II: LIST OF INTENDED USES

1. PRODUCT TYPE 6

The product is intended to be incorporated by industrial users into fuels to act as a preservative. The biocidal product is incorporated into fuels during the formulation process.

The evaluated use of the preserved fuel is use by professional and non-professionals/general public during the refuel of engines.

Table 3.1-2: Acceptable intended uses of the in-can preservative CONTRAM™ ST-1

PT		PT 6 In-can preservative
Formu-lation	**Type**	Liquid: a.s. as manufactured
	Conc. of a.s. in b.p.	100%w/w a.s.
Field of use envisaged		The preservative is added automatically during the formulation of fuels
User		Professional
Target Organisms		gram negative bacteria
Likely amount at which the a.s. will be used (all fields	**Method of application**	The preservative is added during the formulation of fuels
	Applied amount of product	0.01-0.1 % b.p is added directly to fuels
	Application rate of a.s.	Concentration of b.p. in fuels: 0.01-01%
	Number of treatments per year	n.a.
	Typical size of application area	n.a.
Limitations		The applied risk management measures preventing inhalation exposure of men during formulation of fuels (use of b.p.) and fuelling of engines (use of fuel) must be efficient enough to reduce the MBM concentration in air to concentrations below 0.75 mg/m^3 (AEC).

2. PRODUCT TYPE 13

The product is intended to be incorporated by professional users into water based emulsifiable metalworking fluids (MWF) at a concentration of 0.15% w/w a.s. to act as a preservative. The product is intended to prevent the growth of gram negative bacteria in water miscible metal working fluids (MWF). The biocidal product is either incorporated directly into the MWF or incorporated into the lubricant concentrate at a concentration of 3% w/w a.s. before application into the MWF.

It is noted that only a concentration of 5% w/w lubricant concentrate (containing 3% w/w of the product) in water will lead directly to a MBM-concentration of 0,15% w/w in the ready to use dilution of the MWF. Dilutions of e.g. 2% w/w lubricant concentrate (containing 3% w/w of the product) in water (regularly used in grinding processes) will only lead to a MBM-concentration of 0,06% w/w, whereas dilutions of e.g. 10% lubricant concentrate (containing 3% w/w of the product) in water (sometimes used in drilling or sawing processes) will lead to a MBM-concentration up to 0,3% w/w. The correct dilution range should be stated in the product information or in the material safety data sheet of the lubricant concentrate (e.g. recommended dilutions 3% w/w to 6% w/w for a lubricant concentrate containing 3 % w/w of the product).

Table 3.2-2: Acceptable intended uses of the metal working fluid preservative CONTRAM™ ST-1

PT		PT 13 Metalworking fluid preservative
Formu -lation	**Type**	Liquid: a.s. as manufactured
	Conc. of a.s. in b.p.	100%w/w a.s.
Field of use envisaged		1. Use in lubricant concentrate 2. Ready to Use concentration in water based emulsifiable metalworking fluids
		Professional
Target Organisms		gram negative bacteria
Likely amount at which the a.s. will be used (all fields of use envisaged)	**Method of application**	The preservative is added to lubricant concentrate or metalworking fluid
	Applied amount of product	1. Use in lubricant concentrate: typically 3% w/w a.s. 2. Use concentration in metalworking fluid: typically 0.15% w/w a.s.
	Application rate of a.s.	1. Use in lubricant concentrate: typically 3% w/w a.s. 2. Use concentration in metalworking fluid: typically 0.15% w/w a.s.
	Number of treatments per year	Regularly or occasionally re-dosed if a.s. is below effective concentration of 0,15% w/w
	Typical size of application area	n.a
Limitations		• The applied risk management measures preventing inhalation exposure of men during the covered formulation processes must be efficient enough to reduce the MBM concentration in air to concentrations below 0.75 mg/m^3 (AEC) and formaldehyde concentrations in air to concentrations below 0.12 mg/m^3 (AEC), respectively. • The use of prepared metal working fluids is limited to closed or at least partially closed chamber systems and presence of LEV. • The lubricant concentrate containing 3% w/w of the product shall only be applied in such a rate to the MWF in use that the final concentration shall reach 0,1% w/w to 0,15% w/w (which will be reached approximately at dilutions between 3% w/w and 6% w/w of the lubricant concentrate in water)

APPENDIX III: LIST OF STUDIES

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. For studies marked Yes(i) data protection is claimed under Article 12.1(c) (i), for studies marked Yes(ii) data protection is claimed under Article 12.1(c) (ii). These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

LIST OF STUDIES FOR THE ACTIVE SUBSTANCE – SORTED BY SECTION NUMBER

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
A2.7/01	2009	Purity of N,N-Methylenebismorpholine (CONTRAM™ ST-1). [redacted], November 2009, 18p. [redacted], unpublished	Y		Lubrizol
A 2.7/02	2009	Analytical report: Determination of the water content of different batches CONTRAMTM ST-1: 4,4'-Methylenebismorpholine, N, N'- Methylenebismorpholine, Bismorpholinomethane, Methylen-bistetrahydro-1,4-oxazine (CAS# 5625-90-1) [redacted], July 2009, 5p. [redacted], unpublished	Y		Lubrizol
A2.8	2009a	Determination of "free" formaldehyde in the active substance N,N-Methylenbismorpholine: Evaluation of analytical reports. [redacted], November 2009,	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		19p [redacted], unpublished			
A2.10_02	2007	Estimation of the Environmental Concentrations and the Preliminary Environmental Risk Assessment of "N,N-Methylene¬bismorpholine" for life-cycle step production as well as biocidal use as in-can preservative in fuels (PT 6) and as preservative of metal-working fluids (PT 13). [redacted], 20.7.2007 [redacted] applicable, unpublished	Y		Lubrizol
A2.10_01a	2007	Medical statement for formaldehyde-releasing active ingredients [redacted], unpublished	Y		Lubrizol
A2.10_01b	2007	Statement of compliance to all maximum permissible workplace exposures	Y		Lubrizol
A3.1.1	2001	OS 157340: Determination of General Physico-chemical Properties [redacted], unpublished	Y		Lubrizol
A3.1.3	2007	Determination of the Density of CONTRAM™ ST-1. [redacted], unpublished	Y		Lubrizol
A3.2a	2001	OS 157340: Determination of Vapour Pressure [redacted]	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		[redacted], unpublished			
A3.2b	2005	Estimation of physical chemical properties of N,N-Methylenebismorpholine using EpiSuite 3.12 [redacted], published	Y		Lubrizol
A3.4/01	2007	UV Spectrum of CONTRAM™ ST-1. [redacted], July 3, 2007 [redacted], unpublished	Y		Lubrizol
A3.4/02	2007	Determination of the Infrared (IR) Spectrum of CONTRAM™ ST-1. [redacted], Hamburg 17.12.2007 [redacted], unpublished	Y		Lubrizol
A3.4/04	2007	Mass-Spectrum [redacted], unpublished	Y		Lubrizol
A3.4/05		1-H Spektren	Y		Lubrizol
A3.4/06		13-C Spektren	Y		Lubrizol
A3.6b	2007	Determination of the pH-Value of CONTRAM™ ST-1. [redacted], Hamburg July 4, 2007 [redacted], unpublished	Y		Lubrizol
A3.6a	2006	Estimation of the dissociation constants of N,N-Methylolmorpholine by using QSAR ACD/pKa DB, Product Version 10.01, 8.12.2006 [redacted], unpublished	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
A3.7a	2006	Determination of the Solubility Range of CONTRAM™ ST-1: N,N'-methylenebismorpholine (CAS# 5625-90-1) in n-Heptane Using a Turbidimetric Method. [redacted], January 13, 2006 [redacted], unpublished	Y		Lubrizol
A3.7b	2007	Solubility of CONTRAM™ ST-1, N,N'-methylenebismorpholine (CAS# 5625-90-1) in various organic solvents. [redacted], June 29, 2007 [redacted], unpublished	Y		Lubrizol
A3.10	2007	Safety-related evaluation of the thermal stability of "CONTRAM(TM) ST-1 BC 6005 / 100500234". [redacted], unpublished	Y		Lubrizol
A3.12	2008	Determination of the Flash Point (COC) of Contram™ ST-1. [redacted] Hamburg February 12, 2008 [redacted], unpublished	Y		Lubrizol
A3.14	2007	Determination of the Viscosity of Contram™ ST-1 [redacted], Hamburg July 13, 2007 [redacted], unpublished	Y		Lubrizol
A3.17	2007	Reactivity towards container material: CONTRAMTM ST-1. [redacted], 1907.2007	Y		Lubrizol
A4.1/01	2005b	Chargenvergleich des Biozids ST-1. [redacted], 30.8.2005 Revision	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		17.11.2009 & elaborated spectra [redacted], unpublished			
A4.1/02	2008	Validation of the method: Determination of the Formaldehyde content of different concentrations of CONTRAM™ ST-1 (N, N'-Methylenebismorpholine) (CAS# 5625-90-1) Internal report, 20.02.2008, [redacted], unpublished	Y		Lubrizol
A4.1/03	2005a	Produktcharakterisierung des Biozids ST-1. [redacted], 30.6.2005 Revision 16.11.2009 [redacted], unpublished	Y		Lubrizol
A6.1.1	2000	OS157340:Acute oral toxicity in the rat – acute toxic class method. [redacted], unpublished	Y		Lubrizol
A6.1.2	2001	Statement of non performance of dermal toxicity study in the rat. [redacted] 03 April 2001	Y		Lubrizol
A6.1.4	2001	OS157340: Acute dermal irritation in the rabbit. [redacted], unpublished	Y		LUB
A6.1.5	2001	OS157340, Skin sensitisation to the guinea-pig (Magnusson & Kligman method). [redacted]	Y		LUB

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		[redacted], unpublished			
A6.2_01	2007	The in vitro percutaneous absorption of radiolabelled ST-1 through human skin. [redacted], unpublished	Y		LUB
A6.2_02	2007a	*Toxicokinetics of the formaldehyde donor ST-1 in rats after intratracheal instillation. Interim Report: Results with N,N'-Methylenebis[U-^{14}C]morpholine.* [redacted] *,unpublished*	Y		Lubrizol
A6.2_02	2007b	*Toxicokinetics of the formaldehyde donor ST-1 in rats: Pre-Study with intratracheal instillation.* [redacted] *,unpublished*	Y		Lubrizol
A6.3.1	2002	*OS 157340: Ninety day repeated dose oral (gavage) toxicity study in the rat.* [redacted] *, unpublished*	Y		Lubrizol
A6.4.1	2002	OS 157340: Ninety day repeated dose oral (gavage) toxicity study in the rat. [redacted], unpublished	Y		Lubrizol
A6.4.1	2002	OS 157340: 90-day oral toxicity study in the rat. Further comments on the histopathological findings [redacted], unpublished	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
A6.6.1	2000	OS157340: Reverse mutation assay "Ames test" using Salmonella typhymurium and Escherichia coli. [redacted], unpublished	Y		Lubrizol
A6.6.2	2001	*OS157340: Chromosome aberration test in CHL cells in vitro.* [redacted] *, unpublished*	Y		Lubrizol
A6.6.3	2001	OS157340: L5178 TK+/- mouse lymphoma assay. [redacted], unpublished	Y		Lubrizol
A6.6.4	2001	OS157340: Micronucleus test in the mouse. [redacted], unpublished	Y		Lubrizol
A6.6.5	2002	*OS157340: In vivo liver unscheduled DNA synthesis (UDS) assay.* [redacted] *, unpublished*	Y		Lubrizol
A6.8.1	2005	*Oral Prenatal developmental toxicity test with Biozid ST-1 in New Zealand White rabbits.* [redacted] *, unpublished*	Y		Lubrizol
A6.12	2007	Medical statement for formaldehyde-releasing	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		active ingredients [redacted], unpublished			
A7.1.1.1.1 /01	2001	OS 157340: Determination of General Physico-chemical Properties [redacted], unpublished	Y		Lubrizol
A7.1.1.1.1 /02	2005a	Produktcharkterisierung des Biozids ST-1 [redacted], June 2005 [redacted], unpublished	Y		Lubrizol
A7.1.1.1.1 /02	2005b	Chargenvergleich des Biozids ST-1 [redacted], 30.8.2005 [redacted], unpublished	Y		Lubrizol
A7.1.1.1.1 /02	2007	Hydrolysis study in dependance of pH, temperature and concentration [redacted] 2007 (in German; Hydrolysestude bei verschiedenen pH-Werten, Konzentrationen und Temperaturen) [redacted] 22.3.2007, 1.Nachtrag 22.5.2007, 2.Nachtrag 11.6.2007 [redacted], unpublished	Y		Lubrizol
A7.1.1.1.2	1998	Fate, Transport and Transformation Test Guidelines OPPTS 835.2210 “Direct Photolysis Rate in Water by Sunlight”. [redacted], January	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		1998. [redacted], published			
A7.1.1.2.1	2001	OS 157340: Assessment of ready biodegradability; CO_2 Evolution Test [redacted], unpublished	Y		Lubrizol
A7.1.3	2001	OS 157340: Determination of General Physico-chemical Properties [redacted], unpublished	Y		Lubrizol
A7.1.3	2005	Estimation of the adsorptions coefficient of N,N-Methylenebismorpholine using KOWWIN v1.67 [redacted], published	Y		Lubrizol
A7.3.1	2005	EPIWIN 3.12 estimation for N,N-Methylenebismorpholine [redacted], published	Y		Lubrizol
A7.4.1.1	2001	OS 157340: Acute Toxicity to Rainbow Trout (*Oncorhynchus Mykiss* [redacted], unpublished	Y (Exist./First/)		Lubrizol
A7.4.1.2	2001	OS 157340: Acute Toxicity to *Daphnia Magna* [redacted], unpublished	Y		Lubrizol
A7.4.1.3	2001	OS 157340: Algal Inhibition Test [redacted]	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 st submission	Owner
		[redacted], unpublished			
A7.4.1.4	2001	OS 157340: Assessment of the Inhbitory Effect on the respiratipon of activated Sewage Sludge [redacted], unpublished	Y		Lubrizol
A7.4.3.4	2007	Study on the Chronic Toxicity towards Daphnia of „ST-1" according OECD-Guideline No. 211 *(Daphnia magna* Reproduction Test) [redacted], unpublished	Y		Lubrizol
A7.4.3.4	2009	Purity of N,N-Methylenebismorpholine (Contram ST-1 [redacted], Nov. 2009 18p.	Y		Lubrizol

LIST OF STUDIES FOR THE BIOCIDAL PRODUCT – SORTED BY SECTION NUMBER

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 submission	Owner
B2.1.1	2008	Statement about the unchanged and consistent production of Contram ST-1 [redacted], unpublished	Y		Lubrizol
B3.1.1	2001	OS 157340: Determination of General Physico-chemical Properties [redacted], unpublished	Y		Lubrizol
B3.4	2008	Determination of the Flash Point (COC) of Contram™ ST-1. [redacted], unpublished	Y		Lubrizol
B3.5a	2007	Determination of the Alkalinity of CONTRAM™ ST-1. [redacted], unpublished	Y		Lubrizol
B3.5b	2007	Determination of the pH-Value of CONTRAM™ ST-1. [redacted], unpublished	Y		Lubrizol
B3.6	2007	Determination of the Density of CONTRAM™ ST-1. [redacted], unpublished	Y		Lubrizol
B3.7/01	2007a	Stabilitätsuntersuchungen von N-Methylenbismorpholin. [redacted], unpublished	Y		Lubrizol
B3.7/02	2007b	Safety-related evaluation of the thermal stability of "CONTRAM(TM) ST-1 BC 6005 / 100500234". [redacted]	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 submission	Owner
		[redacted], unpublished			
B3.7/03	2007c	Reactivity towards container material: CONTRAMTM ST-1. [redacted], 1907.2007	Y		Lubrizol
B3.11	2007	Determination of the Viscosity of CONTRAM™ ST-1. [redacted], unpublished	Y		Lubrizol
B5.10.2/01	2009	Bacteriostatic activities of the preservative CONTRAM ST-1. Evaluation of the Minimal Inhibition Concentration (MIC) of biocides in accordance with the standard guidelines of the "Deutsche Gesellschaft für Hygiene und Mikrobiologie" (DGHM, 2001-09-01). [redacted] Report date 06.02.2003, revised 16.09.2009 [redacted], unpublished	Y		Lubrizol
B5.10.2/02	2009	Bacteriostatic activities of the preservative CONTRAM ST-1. Evaluation of the Minimal Inhibition Concentration (MIC) of biocides in accordance with the standard guidelines of the "Deutsche Gesellschaft für Hygiene und Mikrobiologie" (DGHM, 2001-09-01). [redacted]; Report date 12.12.2005, revised 16.09.2009 [redacted], unpublished	Y		Lubrizol
B5.10.2/03	2009	Bacteriostatic activities of the preservative CONTRAM ST-1. Evaluation of the Minimal Inhibition Concentration (MIC) of biocides in accordance with the standard guidelines of the "Deutsche Gesellschaft für Hygiene und Mikrobiologie" (DGHM, 2001-09-01). [redacted]	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 submission	Owner
		[redacted] Report date 14.06.2006, revised 14.08.2009 [redacted], unpublished			
B5.10.2/04	2009	Fungistatic activities of the preservative CONTRAM ST-1. Evaluation of the Minimal Inhibition Concentration (MIC) of biocides in accordance with the standard guidelines of the "Deutsche Gesellschaft für Hygiene und Mikrobiologie" (DGHM, 2001-09-01). [redacted]; Report date 14.06.2006, revised 14.08.2009 [redacted], unpublished	Y		Lubrizol
B5.10.2/05	2005	Efficacy of biocides against *Mycobacterium immunogenum*. Cribbs, C., [redacted] Report date 30.09.2005 [redacted] unpublished	Y		Lubrizol
B5.10.2/06	2009	Antimicrobial effectiveness of the biocide CONTRAM ST-1 in a contaminated metal working fluid (MWF). [redacted] Report date 29.05.2006, revised 23.09.2009 [redacted], unpublished	Y		Lubrizol
B5.10.2/07	2006	Biozid ST-1 – Evaluation of biocide efficacy in diesel-water emulsion fuel in the presence and absence of 5% rape seed methyl ester, [redacted] Report date 07.03.2006 [redacted], unpublished	Y		Lubrizol
B5.10.2/08	2010	Evaluation of Biocide Efficacy in Metal Working Fluids in the	Y		Lubrizol

Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Date of 1 submission	Owner
		Presence and Absence of CONTRAM TM ST-1 [redacted] Report date 21.09.2010 [redacted], unpublished			
B5.10.2/09	2010	Evaluation of Biocide Efficacy in Diesel-Water Emulsion Fuel in the Presence and Absence of CONTRAM TM ST-1 [redacted] Report date 11.11.2010 [redacted], unpublished	Y		Lubrizol
B7.1 PT6	2007	Estimation of the Environmental Concentrations and the Preliminary Environmental Risk Assessment of "N,N-Methylenebismorpholine" for life-cycle step production as well as biocidal use as in-can preservative in fuels (PT 6) and as preservative of metal-working fluids (PT 13). [redacted], 20.7.2007 [redacted], unpublished	Y		Lubrizol

APPENDIX IV-1: STANDARD TERMS AND ABBREVIATIONS

Note: The technical terms “active ingredient” and “active substance” are equivalent

Stand. Term / Abbreviation	Explanation
A	ampere
Ach	acetylcholine
AchE	acetylcholinesterase
ADI	acceptable daily intake
ADME	administration distribution metabolism and excretion
ADP	adenosine diphosphate
AE	acid equivalent
AEC	acceptable exposure concentration [mg/m^3 air]
AEL	acceptable exposure level [mg/kg bw day]
AF	assessment factor
AFID	alkali flame-ionisation detector or detection
A/G	albumin/globulin ratio
Ai	active ingredient
ALD_{50}	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
Ann.	Annex
AOEL	acceptable operator exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
As	active substance

Stand. Term / Abbreviation	Explanation
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BAF	bioaccumulation factor
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BP	Biocidal Product
BPD	Biocidal Products Directive
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathy
BSP	bromosulfophthalein
Bt	*Bacillus thuringiensis*
Bti	*Bacillus thuringiensis israelensis*
Btk	*Bacillus thuringiensis kurstaki*
Btt	*Bacillus thuringiensis tenebrionis*
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degrees Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving

Stand. Term / Abbreviation	Explanation
	format)
CAS	Chemical Abstracts Service
Cd	candela
CDA	controlled drop(let) application
cDNA	complementary DANN
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
CSF	Confidential Statement of Formula
Cv	ceiling value
d	day(s)
DES	diethylstilboestrol
DIS	draft international standard *(ISO)*
DFR	Dislodgeable Foliar Residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days post inoculation
DRES	Dietary Risk Evaluation System
DRP	detailed review paper *(OECD)*
DSC	Differential scanning

Stand. Term / Abbreviation	Explanation
	calorimetry
$DT_{50(lab)}$	period required for 50 percent dissipation (under laboratory conditions) (define method of estimation)
$DT_{90(field)}$	period required for 90 percent dissipation (under field conditions) (define method of estimation)
dw	dry weight
DWEL	Drinking Water Equivalent Level
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
E_bC_{50}	median effective concentration, biomass
E_rC_{50}	median effective concentration, growth rate
EC_{50}	median effective concentration
ECD	electron capture detector
ED_{50}	median effective dose
EDI	estimated daily intake
EEC	Estimated Environmental Concentration
EINECS	European inventory of existing commercial substances
ELINCS	European list of notified chemical substances
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EN	European norm
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
EPMA	electron probe micro-

Stand. Term / Abbreviation	Explanation
	analysis
ERL	extraneous residue limit
ESPE46/51	evaluation system for pesticides
EUSES	European Union system for the evaluation of substances
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FBS	full base set
FDA	Food and Drug Administration
FELS	fish early-life stage
FIA	fluorescence immuno-assay
FID	flame ionisation detector
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
F_{mol}	fractional equivalent of the metabolite´s molecular weight compared to the active substance
FOB	functional observation battery
f_{oc}	organic carbon factor (compartment dependent)
Fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
G	gram(s)
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMM	genetically modified micro-organism
GMO	genetically modified organism
GPC	gel-permeation chromatography
GPS	global positioning system
GRAS	Generally Recognized As Safe as designated by FDA
GSH	glutathione
GV	granulosevirus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value)
ha	hectare(s)
HA	Health Advisory
Hb	haemoglobin
HC5	concentration which will be harmless to at least 95 % of the species present with a given level of confidence (usually 95 %)
HCG	human chorionic gonadotropin
Hct	haematocrit

Stand. Term / Abbreviation	Explanation
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionisation detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_S	Shannon-Weaver index
Ht	haematocrit
HUSS	human and use safety standard
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilisation concentration or median inhibitory concentration 1
ICM	integrated crop management
ID	ionisation detector
IEDI	international estimated daily intake
IGR	insect growth regulator
Im	intramuscular
Inh	inhalation
INT	2-p-iodophenyl-3-p-nitrophenyl-5-phenyltetrazoliumchloride testing method
Ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
IUCLID	International Uniform Chemical Information Database
iv	intravenous
IVF	*in vitro* fertilisation
k *(in combination)*	kilo
k	rate constant for biodegradation
K	Kelvin
Ka	acid dissociation constant
Kb	base dissociation constant
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
kg	kilogram
K_H	Henry´s Law constant (in atmosphere per cubic metre per mole)
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	solid-water partition coefficient
kPa	kilopascal(s)
l, L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity

Stand. Term / Abbreviation	Explanation
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD	Lethal Dose-low
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
LEL	Lowest Effect Level
Ln	natural logarithm
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOC	Level of Concern
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
Log	logarithm to the base 10
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
M	metre
M	molar
µm	micrometer (micron)

Stand. Term / Abbreviation	Explanation
MAC	maximum allowable concentration
MAK	maximum allowable concentration
MATC	Maximum Acceptable Toxicant Concentration
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCLG	Maximum Contaminant Level Goal
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
MIC	minimum inhibitory concentration
min	minute(s)
MKC	minimum killing concentration
mL	millilitre
MLD	median lethal dose
MLT	minimum lethal time
mm	millimetre
MMAD	mass median aerodynamic diameter
mo	month(s)
MOE	margin of exposure
mol	mole(s)
MOS	margin of safety
Mp	melting point
MP	Manufacturing-Use Product
MPI	Maximum Permissible Intake
MRE	maximum residue

Stand. Term / Abbreviation	Explanation
	expected
MRID	Master Record Identification (number).
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MT	material test
MW	molecular weight
n.a., N/A	not applicable
n-	normal (defining isomeric configuration)
N	number of observations
NAEL	no adverse effect level
Nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
Ng	nanogram
Nm	nanometre
NMR	nuclear magnetic resonance
no, n°	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOE_rC	no observed effect concentration, growth rate
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPDES	National Pollutant Discharge Elimination System
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OEL	occupational exposure limit
OH	hydroxide
OJ	Official Journal
OM	organic matter content
OP	Organophosphate
OPP	Office of Pesticide Programs
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
PADI	Provisional Acceptable Daily Intake
PAM	Pesticide Analytical Method
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water

Stand. Term / Abbreviation	Explanation
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PIC	prior informed consent
Pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the acid dissociation constant
pKb	negative logarithm (to the base 10) of the base dissociation constant
PNEC	predicted no effect concentration (compartment to be added as subscript)
Po	by mouth
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
PPP	plant protection product
ppq	parts per quadrillion (10^{-24})
Ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PRN	Pesticide Registration Notice
PT	product type
PT(CEN)	project team CEN
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
Q*1	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
QA	quality assurance
QAU	quality assurance unit
(Q)SAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RA	risk assessment
RBC	red blood cell
RED	Reregistration Eligibility Decision
REI	restricted entry interval
RENI	Registry Nomenclature Information System
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL_{50}	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	revolutions per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RS	Registration Standard
RSD	relative standard deviation
s	second
S	solubility
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship

Stand. Term / Abbreviation	Explanation
SBLC	shallow bed liquid chromatography
Sc	subcutaneous
Sce	sister chromatid exchange
SCAS	semi-continous activated sludge
SCTER	smallest chronic toxicity exposure ratio (TER)
SD	standard deviation
Se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
S/L	short term to long term ratio
SMEs	small and medium sized enterprises
SOP	standard operating procedures
Sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
Ssp	subspecies
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STER	smallest toxicity exposure ratio (TER)
STMR	supervised trials median residue
STP	sewage treatment plant

Stand. Term / Abbreviation	Explanation
t	tonne(s) (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
T_{25}	tumorigenic dose that causes tumours in 25 % of the test animals
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TC	Toxic Concentration
TCD	thermal conductivity detector
TD	Toxic Dose
TDR	time domain reflectrometry
TG	technical guideline, technical group
TGD	Technical guidance document
TID	thermionic detector, alkali flame detector
TEP	Typical End-Use Product
TER	toxicity exposure ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGAI	Technical Grade Active Ingredient
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography

Stand. Term / Abbreviation	Explanation
TIm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TNsG	technical notes for guidance
TOC	total organic carbon
Tremcard	transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TTC	2,3,5-triphenylterazoliumchloride testing method
TTC	Toxicological-Threshold-of-Concern
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UR	unit risk
UV	ultraviolet
UVC	unknown or variable composition, complex reaction products
UVCB	undefined or variable composition, complex reaction products in biological material
v/v	volume ratio (volume per volume)
Vis	visible
WBC	white blood cell
Wk	week
WP	Wettable Powder
WPS	Worker Protection Standard
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
Yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

APPENDIX IV-2: ABBREVIATIONS OF ORGANISATION AND PUBLICATIONS

Abbreviation	Explanation
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
BBA	German Federal Agency of Agriculture and Forestry
CA(S)	Chemical Abstracts (System)
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CEC	Commission of the European Communities
CEFIC	European Chemical Industry Council
CEN	European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CIPAC	Collaborative International Pesticides Analytical Council Ltd
CMA	Chemicals Manufacturers Association
COREPER	Comite des Representants Permanents
COST	European Co-operation in the field of Scientific and Technical Research
DG	Directorate General
DIN	German Institute for Standardisation
EC	European Commission
ECB	European Chemicals Bureau
ECCO	European Commission Co-ordination
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre

Abbreviation	Explanation
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EEC	European Economic Community
EHC	Environmental Health Criteria
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPAS	European Producers of Antimicrobial Substances
EPFP	European Producers of Formulated Preservatives
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
EWMP	European Wood Preservation Manufacturers
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GRIN	Germplasm Resources Information Network
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
ICBP	International Council for Bird Preservation
ICCA	International Council of Chemical Associations
ICES	International Council for the Exploration of the Seas

Abbreviation	Explanation
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JECFA FAO/WHO	Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
MITI	Ministry of International Trade and Industry, Japan
NATO	North Atlantic Treaty Organization
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Program (USA)
OECD	Organization for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
OPPTS	Office of Prevention, Pesticides and Toxic Substances (US EPA)
OSPAR	Oslo Paris Convention (Convention for the Protection of the Marine Environment of the North-East Atlantic)
PAN	Pesticide Action Network
RIVM	Netherlands National Institute of Public Health and Environmental Protection
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SETAC	Society of Environmental Toxicology and Chemistry
SI	Système International d'Unitès
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UBA	German Environmental Protection Agency

Abbreviation	Explanation
UN	United Nations
UNEP	United Nations Environment Programme
WFP	World Food Programme
WHO	World Health Organization
WPRS	West Palearctic Regional Section
WTO	World Trade Organization
WWF	World Wildlife Fund