Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

4,4'-methylenedimorpholine; [MBM]

EC Number: 227-062-3
CAS Number: 5625-90-1

CLH-O-0000001412-86-94/F

Adopted
4 December 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 4,4'-METHYLENEDIMORPHOLINE; [MBM]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 4,4'-methylenedimorpholine; [MBM]
CAS number: 5625-90-1
EC number: 227-062-3
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	1
Comment received				
MSCA-FR agrees with classification proposal Carc 1B H350, Muta 2 H341 and with the other proposed classification for corrosivity and dermal sensitisation. We have a comment regarding Human information for all the endpoints: please summarize Human data for products of hydrolysis. We also support the MSCA proposal for environmental hazard.				
Dossier Submitter's Response				
An enormous amount of data is available for formaldehyde. The CLH dossier contains the conclusions from the available data, the latter beeing described more detailed in the Annex to the CLH Dossier "Appendix FA Core Dossier" and "Appendix Morpholine". We hope that this approach is satisfactory for the needs of the RAC.				
RAC's response				
Noted and considered for the opinion document.				

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany	Lubrizol Deutschland	Company-Manufacturer	2
Comment received				
See attached paper for additional information. MBM belongs to a category of biocidal actives known as formaldehyde-releasers (or formaldehyde-donors). These substances control microbial activity by the release of formaldehyde when diluted to their effective concentration. The different members of the formaldehyde-releasing biocides category exhibit different release characteristics and these are dependent on several factors including amongst others the type of chemical structure (N-formal or O-formal), the concentration of biocide, the dilution needed for hydrolysis and fluid pH. MBM contains one of the lowest levels of total 'releasable' formaldehyde per molecule (16% w/w) within the entire category of formaldehyde-releasers.				

MBM has been on the market in the EU since the early 1990s and is used to control bacterial growth in water-based metalworking fluids and fuel at a maximum end use fluid concentration of 1500 ppm. MBM as manufactured is 98.5% by weight MBM with the remaining trace components comprising N-methylolmorpholine, morpholine, water and 'free' (unbound) residual formaldehyde that is present at less than 0.005% (50 ppm) by weight. MBM has low volatility (low vapour pressure and Henry's Law Constant) and is considered to be stable in MWF concentrations and end use fluids with a half-life in terms of months.

Occupational measurements and measurement of the stability of MBM in end use fluids, which were not included in the Competent Authority Report that was submitted to the Biocidal Products Committee, are presented in this paper. These demonstrate that the MBM molecule is relatively stable in the form in which it is "reasonably expected to be used" (i.e. its intended use) and which would potentially result in the highest exposure of workers to the non-volatile MBM molecule via aerosolisation, with a half-life estimated to be 5-8 months in an end use metalworking fluid emulsion. This contrasts significantly with the hypothesis used to justify the proposed harmonised classification of MBM as a carcinogen, mutagen and sensitiser that sufficient formaldehyde would be released from the MBM molecule by contact with moisture from workers' nasal mucosa or skin to cause an adverse toxicological event. Critically, it also demonstrates that all 'bound' formaldehyde is not released instantaneously upon contact with water in the end use fluid. Measurements of worker exposure to airborne formaldehyde and oil mist in a metalworking machining workshop utilising a fluid containing MBM demonstrate that the real-life exposure to either 'released' formaldehyde via volatilisation or MBM by aerosolisation will be negligible under conditions of normally expected use. This information, as well as consideration of published work suggesting that the nasal mucosa that is proposed to be responsible for the release of formaldehyde from MBM by hydrolysis upon contact following inhalation may also provide a partial barrier to direct contact with tissue means therefore that there will be insufficient exposure (bioavailability) to MBM by the inhalation route to give scientific credibility to the classification proposal based on total releasable formaldehyde; in summary, the data presented in this paper clearly demonstrates that inhalation exposure of workers to MBM is negligible and de minimis as supported by its physico-chemical properties, its intended reasonable use, its relative stability in an end use fluid, data from a UK Exposure Study, and based on arguments contained in an earlier risk assessment that used conservative models (e.g., for notification in Belgium where a product comprising 100% MBM is approved until 2024).

With regard to carcinogenicity in particular, there is no credible scientific evidence that MBM is a carcinogen. No carcinogenicity studies have been conducted with MBM and there is significant weight-of-evidence that MBM is not inherently a carcinogen. MBM is not genotoxic in vivo following oral administration indicating that MBM is not expected to be carcinogenic, at least by a primary genotoxic mechanism. Additionally, Quantitative Structure Activity Relationship (QSAR) analysis of the MBM molecular structure by the OECD methodology presents no alerts for carcinogenicity (or mutagenicity) and no histopathological findings such as hyperplasia or neoplastic lesions were observed in the 90 day oral gavage study with rats or in the oral prenatal developmental toxicity study on MBM. Finally, the final concentration of released formaldehyde in an end use fluid (both calculated and measured) is well below the regulatory threshold for classification of substances and mixtures as a carcinogen (i.e. << 0.1%, <<1000 ppm) and below the level (i.e. 2 ppm) previously recognised by RAC as resulting in no significant effects over the course of MBM's intended use.

With the exception of skin irritation/corrosion hazard classification, the current harmonised classification proposal is entirely reliant on the assumption by the evaluating Competent

Authority that there is rapid hydrolysis of MBM in contact with moisture to instantaneously release 'bound' formaldehyde, such that sufficient formaldehyde reaches relevant biological tissues to exert an adverse toxicological effect. The information presented in this paper demonstrate that this is a significant oversimplification of what happens when MBM (or another formaldehyde donor) is used in the workplace (i.e. in the form that it is placed on the market or can reasonably be expected to be used). While the RAC has previously considered hydrolysis by-products when assessing the hazard classification of other substances, it has done so in the context of specific acute inhalation hazard associated with its intended use (e.g. metal phosphides generating phosphine gas for use as a fumigant). The release characteristics demonstrated by MBM in aqueous metalworking fluid emulsions under in-use conditions means that a similar approach is not justified in this case, especially for the proposed classification as a carcinogen which relies on chronic exposure of workers' nasopharyngeal epithelium to sufficient 'released' formaldehyde (i.e. at a supra-threshold level).

The current harmonized classification proposal for MBM based on releasable formaldehyde is therefore neither robust nor scientifically defensible; it does not reflect the intrinsic properties of the molecule, the supporting experimental data, its reasonable use, weight of evidence, and is not therefore in accordance with the EU CLP Regulation.

ECHA comment: The following non-confidential attachment was provided with this comment. See also comments 7, 11 and 18 [see Attachment 2 and 3]

- *Harmonised classification and labeling proposal for N,N'-methylene bismorpholine (MBM) - Lubrizol comments for the public consultation*
- *Occupational Exposure to Formaldehyde from Metalworking Fluids Containing the Antimicrobial Agent Methylenebismorpholine*

The following confidential attachment was provided with this comment. See also comments 7, 11 and 18 [see Attachment 1 – confidential section]

- *TRW study report.pdf*

Dossier Submitter's Response

The physical form of MBM was respected for the assessment: MBM is marketed as concentrated liquid and diluted to concentrations relevant for application. For liquids respiratory exposure via aerosols is in principle possible, in addition the vapour pressure of MBM is estimated to be above 0.1Pascal, respiratory exposure scenarios considering this are presented in the draft Biocides Competent Authority Report (draft CAR). (The CLH Dossier contains only the hazard assessment, the draft CAR includes besides the hazard assessment also exposure and risk assessment)

Also the new exposure data referenced in the comment demonstrate obviously the release and presence of formaldehyde at sites due to the hydrolysis of MBM. Choice of operational conditions and risk management measures are important parameters for keeping release of formaldehyde at a low level and can result in higher levels, if they are not optimized. Referring to the provided data, it is acknowledged, that mwf-solution might release more slowly and lower amounts of formaldehyde than solutions containing aqueous formaldehyde only. Nevertheless, referring also to the referenced data, formation of formaldehyde cannot be disregarded for the indended use and occurs at relevant levels requiring adaption of operational conditions and risk management measures. The actual Biocides draft CAR indicates an acceptable risk for human health for the intended uses described in the Biocides draft CAR.

Anyway classification must focus on the intrinsic property of the substance and in our view

the available data lead inevitably to classification for Carc. Cat 1B referring to the release and presence of formaldehyde. CLP Regulation, Annex I, article 3.6.2.2.1 states that "Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data." Formaldehyde release is an intrinsic property of the formaldehyde releaser.

The human medical data for MBM were summarized by the applicant in document IIIA6.12.1-8, evaluated by the RMS and attached to the Biocides draft CAR as well as the CLH report. These human medical data do not indicate concern for carcinogenicity – which supports that human exposure is not in a range of obvious, immediate concern. Not representing powerful epidemiology studies, they cannot provide evidence for the absence of hazard or risk. In addition the RAC classification for formaldehyde is based on limited evidence in humans and sufficient evidence in animal studies. No experimental carcinogenicity data are available for MBM, consequently these were read across from formaldehyde, based on mechanistic toxicological considerations

Chapter 2.2. of the draft CLH report explains: "Formaldehyde is classified as Carcinogen Cat 1B (via inhalation) and Mutagenicity Cat 2 on the basis of available animal and human data. No carcinogenicity data are available for MBM, but mutagenicity data are comparable with formaldehyde. MBM is proposed to be classified for carcinogenicity cat 1B and mutagenicity cat 2 based on the mechanistic considerations of total releasable amount of formaldehyde upon contact with biological media and read across of the carcinogenic and mutagenic property of formaldehyde. Alternatively MBM may not be classified for carcinogenicity and mutagenicity based on considering just the amount of free formaldehyde in MBM. Supportive arguments for both options are provided in the specific chapter on carcinogenicity." Instantaneous release of formaldehyde from the releaser upon contact with water is neither necessary nor used as the basis of arguing for classification. However it is clear that in the presence of organic material and minimal amounts of water, as is the case at any site of contact with biological tissue, the small amount of hydrolyzed formaldehyde will react with the biological material and the equilibrium will shift towards new release of formaldehyde. This is also the principle of the biocidal activity. In fact also the skin corrosion study with the undiluted MBM as well as the pre-test to the skin sensitization study using a 20% dilution of MBM (to test concentrations inducing necrosis/irritation) document the biological reactivity of the formaldehyde releaser. Also the dermal absorption study and the intratracheal instillation study with MBM indicate formaldehyde release after contact with the biological media. The available hydrolysis data just indicate that highly concentrated MBM is relatively stable in water and with higher aqueous dilutions MBM hydrolyses to formaldehyde and morpholine (DT50 about 2.4 hours). Further data are available indicating long stability in metal working fluids. However these data do not mirror formaldehyde reactivity and release upon contact with biological tissue. There are no data informing on the exact kinetics of formaldehyde release from contact with biological material. However instantaneous release of formaldehyde from contact with water was neither the explanation for potential carcinogenic effect, nor is it required.

In the absence of carcinogenicity data for MBM, the carcinogenicity data for formaldehyde were used by read across principle. This read accross approach was also used by the applicant as justification for non–submission of carcinogenicity study for the MBM (see attached document Doc III A6_7 MBM non sub.doc). Considering that toxicological testing is usually required up to doses or concentrations where adverse effects can be observed (maximum tolerated dose) and considering that the local irritative and genotoxic effects (at the site of contact) from formaldehyde release are the most critical effects to be expected -

new carcinogenicity data for the reaction product were very unlikely to provide any new toxicological information and therefore due to animal welfare requirements unlawful to require.

Formaldehyde and MBM are considered a local carcinogen. In the presence of a clear biocidal mode of action and knowledge of equilibrium behaviour, hydrolysis and reaction kinetics negative SARs should be disregarded.

In the sub-chronic study and the developmental toxicity study with MBM local effects in the gastrointestinal tract were observed. In principle such effects can develop into tumours upon long term exposure. A genotoxic mode of action contribution cannot be excluded. However for formaldehyde respiratory exposure was observed as the critical route for local tumour development. Respiratory studies with MBM were neither available nor required.

It is not appropriate to consider the final in use concentration of MBM for the classification of the substance. The concentration limit (0.1%) is a fully pragmatic value for the classification of mixtures containing category 1 carcinogens. However for risk assessment the concentration of formaldehydein the higher dilutions of MBM in the end use fluids and the resulting exposure concentration in air are considered and form immanent importance for the risk characterisation of the substance.

As shown in table 4.8-3 and 4.8-4 in the CLH report with regard to mutagenicity the available data for MBM are consistent with the available data for formaldehyde: The data were positive in vitro and negative or ambiguous for systemic genotoxicity in vivo. This similarity supports the read across of the formaldehyde data to MBM. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for MBM no in vivo data for local genotoxicity are available. Furthermore from a mechanistic toxicological point of view the positive in vitro genotoxicity is most likely due to formaldehyde release, i.e. reflects the local genotoxicity of formaldehyde and MBM.

It is true that the genotoxicity classification should primarily be based on the consideration of potential effects in the germ cells, which is explained in chapter 4.8.6. and 4.8.7. of the CLH report. However as explained in chapter 4.8.4 of the CLH report the RAC opinion proposing classification of formaldehyde (from 2012) supported that "due to the induction of genotoxic effects in vivo on somatic cells at site of contact, which are supported by positive findings from mutagenicity and genotoxicity tests in vitro, … classification of formaldehyde for mutagenicity category 2 in accordance with the CLP Regulation, with the hazard statement H341 (Suspected of causing genetic defects) is therefore warranted..." The RAC opinion, referring to the ECHA CLP guidance section 3.5.2.1.2. and 3.5.1., explains that positive in vitro genotoxicity data plus positive in vivo (systemic and/or local) somatic genotoxicity data may support category 2 classification for mutagenicity. Since formaldehyde data were read across to MBM also this harmonized conclusion was suggested for MBM.

The term "precautionary principle" is obviously challenged by the applicant, and in fact it is not needed. The phrase in the CLH report could also have been worded as follows: "The formaldehyde releasing substance should be classified like formaldehyde - based on the considerations of total releasable formaldehyde, intended use, category of users and exposure taking into account the uncertainties in this case of difficulties with the assessment of substances that are instable, showing equilibrium behavior and having half-lives depending on dilution, temperature and/or UVCB characteristics.". The arguments for and against classification for carcinogenicity are comprehensively listed in the CLH Dossier

in table 4.9.-2. Explicit explanation for the classification proposal is also provided in this response to comments table above. These considerations are considered as sufficient basis for the RAC discussion and conclusion for this substance.
On a generic discussion level, as a principal response to a generic conclusion in the FABI legal and regulatory statement ("Discussions related to the precautionary principle therefore have no place in the context of decisions on the classification of substances.") we feel that awareness is needed for the latest WHO work on the uncertainty descriptions of hazard (WHO, Harmonisation Project Document No 4. 2007; WHO, Harmonisation Project Document No 11. 2014) and other related scientific publications (e.g. Paparella et al. 2013 ALTEX, 2013. 30(2): p. 131-44). These publications substantiate that from a purely scientific perspective, uncertainty is an intrinsic element of any science including hazard, exposure and risk assessment.
The skin sensitization study (GPMT) with MBM was negative, but the conclusion was not reliable since no skin irritation was observed with the topical induction with 10% solution in Alembicol D. The pretest-data indicates that the concentration-response relationship for skin irritation to corrosion seems to be steep (1/6 animals showed slight erythema with 1% as well as with 5% topical application; 4/6 animals showing slight erythema with 10% topical application, 4/6 animals showing necrosis with 20% topical application). Formaldehyde reaction with proteins is a local event, translocation of the modified protein to systemic circulation may be subsequent. From the dermal absorption study summarized in the CLH report a 60% to 70% dermal absorption rate was concluded. Details of the study summaries are presented in the Annex to the CLH report. RAC may develop its own opinion how to weight the negative skin sensitization results of the GPMT test of MBM in the context of an overall WoE including knowledge of formaldehyde release at site of contact with biological tissues.

We acknowledge the perspective that formaldehyde releaser products are technically and socioeconomically important. In principle we do not have objections to marketing formaldehyde releasers based on correct classification and labelling, acceptable risk and socioeconomic need.

RAC's response

The Rapporteurs acknowledge the extensive answers given by the DS. With regards to the GMPT test, the result can not be interpreted as negative. See the text in the opionion document.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	3

Comment received

The German CA supports the proposal to classify MBM for Carc. 1B; H350, Muta. 2; H341 and Skin Sens. 1; H317 based on the mechanistic considerations of total releasable amount of formaldehyde upon contact with biological media and read across of properties of formaldehyde. Therefore the classification as proposed by the dossier submitter is, in general, supported.

A classification as Skin Corr. 1 would be preferred instead of sub-categorisation as Skin Corr. 1B as explained below.

Concerning the classification as skin sensitizer, the GCL of 1% is preferred instead of the proposed SCL of 1.2% as explained below.

Concerning the proposed labelling (Precautionary statements) we would like to point out that according to the 4th ATP „P281" will be deleted and replaced by „P280". Based on the

CMR properties the CLH-proposal includes already the quite generic combination P308 + P313. Therefore other similar / more specific precautionary statements ("P310", "P333 + P313") can be omitted. To provide a clearer advice, "P310" should at least be added to the combination "P305 + P351 + P338". As a result, P305 + P351 + P338, P310 should appear on the label.

Dossier Submitter's Response

Skin Corr 1B
Please see our response below to comment 16.

Skin Sens. SCL
In line with an earlier discussion at the BPC WG we agree to delete the SCL and suggest the GCL for MBM.

P-Statements
we agree to change the P statements as proposed by DE.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Finland		MemberState	4

Comment received

We have few editorial comments:
page 39, second paragraph, the sentence "The hydrolysis products…" seems to miss words (genetic effects?).
page 42. We note that since classification is based on intrinsic properties of the chemical, the applicants summary about consequences of classification is not in the scope of the CLH proposal.

Dossier Submitter's Response

OK, we corrected the sentence on page 39.
We support that this supplementary information from the applicant with regard to consequences for classification is transparent for RAC.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	Germany	Verband Schmierstoff-Industrie e.V:	Industry or trade association	5

Comment received

We follow the arguments of the FABI group (attached). MBM (and other formaldehyde releasers) are used in metal working emulsions at a concentration of 0,1%.
MBM (and other formaldeyde releasers) are almost the only biocides left in PT13 for initial protection of metal working fluids from bacteria and thus protect workers health and prolong fluid life to minimize waste.

ECHA comment: The following attachment was provided with this comment [see Attachment 1]:

- *Statement supporting the comments provided by [name of FABI member]concerning the proposed harmonised classification for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)(MBO)*

Dossier Submitter's Response

Please see our response to comment 2.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015		FABI - Formaldehyde Biocides Interest Group	Industry or trade association	6

Comment received

The submission was made on behalf of the members of the Formaldehyde Biocides Interest Group (FABI), producers of formaldehyde releasers participating in the Biocidal Products Regulation (BPR) Review Programme. N,N'-methylenebismorpholine (MBM) belongs to a category of biocidal actives known as formaldehyde releasers. The FABI members provided input to the consultation considering that the classification proposal for MBM could be by analogy applicable for all formaldehyde releasers.

ECHA comment: The following <u>non-confidential</u> attachments were provided with this comment [see Attachments 4 and 5]

- *Legal & Regulatory Statement from FABI members in response to the 45 day public consultation on the proposed harmonised classification of N ,N'-methylenebismorpholine*

- *Statement supporting the comments provided by Lubrizol concerning the proposed harmonised classification for N,N'-methylenebismorpholine (MBM)*

Dossier Submitter's Response

Please see our response to comment 2.

Legal Position of the Austrian eCA to the Legal and Regulatory Statement from FABI Members:

FABI raised concerns that the CLH Report for MBM submitted by the Austrian Competent Authority (the CLH Proposal) is vitiated by fundamental errors of law arising from conclusions not substantiated by the available scientific information, a failure to properly apply the general binding principles of EU law and a failure to properly apply the specific requirements of Regulation (EC) No. 1272/2008 (the CLP Regulation) and its Guidance.

FABI states that the CLH Proposal suffers from specific breaches of the CLP Regulation. It is based on the fictitious presumption that the total amount of formaldehyde present in MBM is "releasable" and ignores the legal requirement that a conclusion as to whether the relevant classification criteria are met must be taken in view of the form of the substance, as it is placed on the market and as can be reasonably expected to be used.

The Austrian eCA strongly refuses these accusations because the proposed CLH Report for MBM applies to the relevant requirements of the CLP Regulation.

The CLP Regulation contains clear provisions on how the classification shall be done and for this purpose the **criteria of Annex I** are of significant importance. Several articles of the CLP Regulation refer to **Annex I**. The following examples are not exclusive:

Art. 3 of the CLP Regulation states that the criteria relating to hazards are laid down in **Parts 2 to 5 of Annex I** and shall be classified in relation to the respective hazard classes provided for in that Annex.

According to Art. 5 of the CLP Regulation a substance shall be identified by the relevant information available or the purposes of determining whether the substance entails a physical, health or environmental hazard as set out in **Annex I**.

Also the **decision** for the classification of substances and mixtures has to be based on criteria of Annex I. If the evaluation pursuant to Article 9 and Article 12 shows that the hazards associated with the substance or mixture meet the criteria for classification in one or more hazard classes or differentiations in **Parts 2 to 5 of Annex I**,

"manufacturers, importers and downstream users shall classify the substance or mixture in relation to the relevant hazard class or classes or differentiations by assigning the following:

(a) one or more hazard categories for each relevant hazard class or differentiation;

(b) subject to Article 21, one or more hazard statements corresponding to each hazard category assigned in accordance with (a)."

Part 3 of Annex I describes health hazards and part 3.6 contains specific requirements for cancerogenicity.

Part 3.6.2.2.1. reads *"Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an **intrinsic property** to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data."*

In compliance with this regulation the Austrian eCA focused the classification of the proposed CLH Proposal on the **intrinsic property** of MBM. The intrinsic property results from the release and presence of **formaldehyde**, which in our view leads inevitably to classification for Carc. Cat 1B referring to the available data.

FABI ignores the clear wording of Annex I, Part 3.6.2.2.1 of the CLP Regulation that classification of cancerogenicity has to be based on the intrinsic property of the substance.

FABI cites several general provisions and recitals of the CLP Regulation but does not make any reference to the **special** provision in Annex I, Part 3.6.2.2.1, which refers **solely to cancerogenicity**. Thus FABI's opinion does not reflect the legal situation concerning classification under the CLP Regulation.

Hence the CLH Proposal is not based on a fictitious presumption but on the clear wording and spirit of Annex I, Part 3.6.2.2.1, of the CLP Regulation.

The Austrian eCA would like to point out another inconsistency in the application for MBM and FABI's argumentation:

The evaluation of carcinogenicity performs on carcinogenicity data for the substance formaldehyde by using the "**read across principle**".

The read across principle can **close data gaps** and is allowed within chemical categories whose physicochemical and human health and/or ecotoxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern, usually as a result of structural similarity.

The read across approach was necessary in the evaluation of MBM because the applicant **did not provide carcinogenicity data** and as a justification for non–submission the applicant itself asked for read across to carcinogenicity data of formaldehyde.

In the view of the Austrian CA the read across principle was acceptable but cannot only close data gaps while being neglected when leading to undesirable consequences in the form of unwanted classifications.

Finally, the Austrian CA holds on to the consistent approach for evaluation and classification of MBM and rejects the accusations made by FABI.

RAC's response

DS reflections are supported. No further response.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany	Lubrizol Deutschland	Company-Manufacturer	7

Comment received

See attached paper for additional information. Based on the data presented in the CLH dossier it cannot be safely concluded that MBM is inherently a carcinogen. Instead, the current classification proposal is based on the concept that MBM results in human exposure that liberates formaldehyde, which is the carcinogenic component. Since the classification proposal is dependent on exposure factors which govern the liberation of formaldehyde, it is therefore essential that such exposure factors are fully taken into account by RAC to assess the degree of potential exposure because they are patently integral to the classification discussion.

In accordance with EU CLP Regulation we strongly suggest that classification of MBM for carcinogenicity is inappropriate based on numerous lines of evidence presented below. Further, in view of the explanation of the hydrolytic stability of MBM in the form that it is placed on the market and the very slow rate of formaldehyde-release (as a proportion of total dosed MBM) during its use as intended i.e. in end use diluted metal working fluids, there is demonstrably no credible scientific justification for classifying MBM as a suspected carcinogen, either in terms of direct evidence or on a weight-of-evidence approach.
1) MBM as manufactured and in the form that it is placed on the market contains significantly less than 0.1% 'free' or 'unbound' formaldehyde as an impurity (measured 'free' formaldehyde was < 50 ppm).

2) CLP states that "carcinogenic potential can be inferred from in vivo and in vitro

…mutagenicity studies". The higher tier in vivo studies demonstrate that MBM is not genotoxic by oral administration.

3) Using the decision logic for classification of substances for carcinogenicity (Guidance on the Application of CLP criteria section 3.6.2.6), when the substances do not have carcinogenicity data then classification as a carcinogen based on actual data is not possible.

CLP states that non testing data for the substance such as QSAR and Read Across predictions can be used when a substance has not been tested for carcinogenicity. In order to evaluate the potential for carcinogenicity according to CLP the OECD Toolbox version 3.2 was used to profile MBM. As shown below, based on QSAR predictions for carcinogenicity as well as read across predictions from chemicals with analogous structures having some experimental data MBM was confirmed to have a very low probability for carcinogenic potential. Thus, MBM should not be classified as a carcinogen based on model data.

Similarly, read-across from formaldehyde to MBM has been demonstrated in this paper to be scientifically unsound because there is no credible evidence to suggest repeated exposure of workers to MBM would release sufficient formaldehyde to cause tumours. On this basis, MBM itself cannot be considered to be inherently carcinogenic in accordance with the classification guidance.

4) The proposed classification of MBM for carcinogenicity relies solely on the carcinogenic effects of released formaldehyde and that a sufficient amount of formaldehyde is released at the nasopharyngeal cell surface to result in tumours at the site of contact. This is because numerous scientific articles and the previous RAC opinion for formaldehyde recognise that there is a concentration below which critical effects and carcinogenicity of formaldehyde have not been demonstrated (e.g., at 2 ppm; RAC 2012). The conclusion that the occurrence of tumours at higher levels is the result of chronic proliferative processes and that the genotoxicity of formaldehyde plays essentially no part in its carcinogenic potential is expertly summarized by Gelbke et al. The published literature also considers exposure to exogenous formaldehyde to be insignificant compared to exposure to endogenously formed formaldehyde, and that in the absence of irritation there are no long term toxicity issues arising from formaldehyde exposure. Finally, the literature confirms that there is essentially no risk to tissues other than those at the local site of contact. (see Bogdanffy et. al. 1987; Casanova-Schmitz et. al. 1984; Heck and Casanova (2004); NRC 2011; Heck et. al. 1985; Tenga et. al. 2001.)
The current proposal to classify MBM as a carcinogen relies entirely on the hypothesis that sufficient formaldehyde would be released rapidly in contact with biological media. This hypothesis, as noted by the proposal, is in "qualitative terms" supported by hydrolysis data generated from MBM/water solutions at very low dilutions. The experimental stability data (Appendix 1) and workshop exposure data (Table 2) presented in this paper actually demonstrate that quantitative application of this data for use in the read across is not appropriate. It should be noted that the RAC has previously concluded that the available data on low dose effects of formaldehyde suggest that the dose-related 'key events' seen below 2 ppm were considered to be non-significant (RAC 2012). Indeed, formaldehyde contact with biological tissue appears to require sufficient levels to trigger an irritant (cytotoxic) and/or cell proliferative response in the nasopharyngeal epithelium leading subsequently to cancers. An irritant/cytotoxic and/or cell proliferation response in the nasopharyngeal epithelium is believed to be a necessary precursor to the development of local tumours in the nasal epithelium (NRC 2011). Thus, being able to demonstrate this with MBM rather than formaldehyde, or at least put forward a credible argument that it occurs, should be a necessary pre-requisite for classifying MBM as a carcinogen
The RAC opinion for formaldehyde (RAC 2012) and that of the US NRC (NRC 2011) also

confirmed that there is no evidence or plausible mechanistic process for any systemic distribution and effect of formaldehyde distant to the site of exposure. As a consequence we consider that there are numerous flaws in the proposal to classify MBM as a carcinogen based on release of total ('bound') formaldehyde following contact with moisture in the nasopharyngeal epithelial mucus layer. Each flaw in the overall hypothesis can be addressed in turn:

1. Most crucially, there is a false assumption that hydrolysis of the MBM molecule occurs immediately upon contact with the nasopharyngeal epithelium and would release sufficient 'bound' formaldehyde leading to release of sufficient 'free' formaldehyde to cause an irritation/cell proliferation response.

Stability data shows that concentrated MBM shows only very slow hydrolysis even when diluted to 50% in water (see Table 1 and Appendix 1). Furthermore, the demonstrated limited hydrolysis of formaldehyde (Priha 1995) and the protein-rich composition of nasopharyngeal mucus (111 proteins have been identified; Casado et al. 2005) suggests that rapid hydrolysis in a fully aqueous matrix in the respiratory system is unlikely. Further, as concentrated MBM is demonstrably corrosive to dermal skin it is reasonable to conclude that occupational exposure of the nasopharyngeal epithelium to neat MBM would result in the destruction of the epithelial cells rather than subtle cytotoxic effects or induction of cell proliferation that would act as the precursor to tumour formation. Similarly, inhalation exposure to low concentrations of MBM for example through aerosolisation of an end-use metalworking fluid containing MBM at the typical effective dose of 1500 ppm would be well below the calculated DNEL for local irritant effects.

2. It is an unrealistic assumption that the nasal epithelium of metalworkers will be exposed to sufficient MBM in the workplace.

MBM is non-volatile (calculated vapour pressure; 0.625 Pa at 25 °C or 0.443 Pa at 20 °C; Section 1.3, Table 9 of the dossier) and there is therefore no possibility of workers throughout the supply chain being repeatedly exposed to the neat substance by inhalation during handling and during any reasonably expected (intended) use due to the non-volatile property of the substance. Additionally, aerosolisation is not a credible route of inhalation exposure to neat MBM during handling by workers when formulating a mixture as insufficient energy would be generated during the formulation process to disperse an aerosol. There is however the possibility of inhalation exposure of metalworkers to dilute levels of MBM due to aerosolisation of an end-use fluid during high energy operations such as grinding, cutting or milling. However, actual workplace measurements show this to be practically irrelevant in terms of delivering sufficient MBM to the workers' respiratory system. Furthermore, this route of exposure (via high energy aerosolisation) would not be appropriate for other approved uses of MBM (e.g. PT6).

3. It is an unrealistic assumption that workers' nasopharyngeal epithelium will be exposed to supra-irritating levels of formaldehyde released from MBM on repeated occasions.

The preponderance of evidence accumulated through numerous studies and repeated analysis of the extensive body of toxicology data indicates that formaldehyde causes localized nasopharyngeal tumours following repeated inhalation exposure by chronic irritation and/or cellular proliferation of the nasopharyngeal epithelium. The recently finalised RAC opinion on the harmonised classification of formaldehyde also agreed that specific cellular mechanisms must occur for formaldehyde to cause nasopharyngeal cancer, and it follows that chronic exposure to sub-irritating levels of formaldehyde does not result in nasopharyngeal tumours (RAC 2012). The exposure data included in this paper clearly demonstrates that exposure of workers' nasopharyngeal epithelium to supra-irritating levels would not happen under conditions of intended and reasonably expected use even in the worst-case occupational environment. As above, chronic irritation of the workforce respiratory system would be required to elicit adverse effects and such conditions would not

be unnoticed or deemed acceptable in an industrial environment.

There is no indirect evidence that MBM is carcinogenic. In addition to there being no evidence of a genotoxic response in whole animals, we have followed ECHA's own CLP guidance for carcinogenicity and critically assessed the other experimental data to seek evidence of pre-neoplastic changes to compensate for the absence of a carcinogenicity study on MBM. In the absence of any pre-neoplastic changes in these studies and in the absence of any genotoxic response in whole animals the weight-of-evidence suggests that MBM is not a carcinogen and therefore there is no scientific justification for its classification as such.

ECHA comment: The following non-confidential attachment was provided with this comment. See also comments 2, 11 and 18 [see Attachment 2 and 3]

- *Harmonised classification and labeling proposal for N,N'-methylene bismorpholine (MBM) - Lubrizol comments for the public consultation*
- *Occupational Exposure to Formaldehyde from Metalworking Fluids Containing the Antimicrobial Agent Methylenebismorpholine*

The following confidential attachment was provided with this comment. See also comments 2, 11 and 18 [see Attachment 1 – confidential section]

- *TRW study report.pdf*

Dossier Submitter's Response

Please see our response to comment 2, which contains all considerations also with regard to this comment No 8.

Here the considerations relevant to this comment 7 are repeated in this respective order.

Formaldehyde release is an intrinsic property of the formaldehyde releaser when it comes into contact with biological material. Therefore in our view the classification-proposal is based on the intrinsic properties of the substance. Moreover the physical form of MBM was respected for the assessment: MBM is marketed as concentrated liquid and diluted to concentrations relevant for application. For liquids respiratory exposure via aerosols is in principle possible, in addition the vapour pressure of MBM is estimated to be above 0.1 Pascal, respiratory exposure scenarios considering this are presented in the draft Biocides Competant Authority Report (draft CAR).

Also the new exposure data referenced in the comment demonstrate obviously the release and presence of formaldehyde at sites due to the hydrolysis of MBM. Choice of operational conditions and risk management measures are important parameters for keeping release of formaldehyde at a low level and can result in higher levels, if they are not optimized. Referring to the provided data, it is acknowledged, that mwf-solution might release more slowly and lower amounts of formaldehyde than solutions containing aqueous formaldehyde only. Nevertheless, referring also to the referenced data, formation of formaldehyde cannot be disregarded for the indended use and occurs at relevant levels requiring adaption of operational conditions and risk management measures. The actual Biocides draft CAR indicates an acceptable risk for human health for the intended uses described in the Biocides draft CAR.

Chapter 2.2. of the draft CLH report explains: "Formaldehyde is classified as Carcinogen Cat 1B (via inhalation) and Mutagenicity Cat 2 on the basis of available animal and human data. No carcinogenicity data are available for MBM, but mutagenicity data are comparable with formaldehyde. MBM is proposed to be classified for carcinogenicity cat 1B and mutagenicity

cat 2 based on the mechanistic considerations of total releasable amount of formaldehyde upon contact with biological media and read across of the carcinogenic and mutagenic property of formaldehyde. Alternatively MBM may not be classified for carcinogenicity and mutagenicity based on considering just the amount of free formaldehyde in MBM. Supportive arguments for both options are provided in the specific chapter on carcinogenicity." Instantaneous release of formaldehyde from the releaser upon contact with water is neither necessary nor used as the basis of arguing for classification. However it is clear that in the presence of organic material and minimal amounts of water, as is the case at any site of contact with biological tissue, the small amount of hydrolyzed formaldehyde will react with the biological material and the equilibrium will shift towards new release of formaldehyde. This is also the principle of the biocidal activity. In fact also the skin corrosion study with the undiluted MBM as well as the pre-test to the skin sensitization study using a 20% dilution of MBM (to test concentrations inducing necrosis/irritation) document the biological reactivity of the formaldehyde releaser. Also the dermal absorption study and the intratracheal instillation study with MBM indicate formaldehyde release after contact with the biological media. The available hydrolysis data just indicate that highly concentrated MBM is relatively stable in water and with higher aqueous dilutions MB hydrolyses to formaldehyde and morpholine (DT50 about 2.4 hours). Further data are available indicating long stability in metal working fluids. However these data do not mirror formaldehyde reactivity and release upon contact with biological tissue. There are no data informing on the exact kinetics of formaldehyde release from contact with biological material. However instantaneous release of formaldehyde from contact with water was neither the explanation for potential carcinogenic effect, nor is it required.

As shown in table 4.8-3 and 4.8-4 in the CLH report with regard to mutagenicity the available data for MBM are consistent with the available data for formaldehyde: The data were positive in vitro and negative or ambiguous for systemic genotoxicity in vivo. This similarity supports the read across of the formaldehyde data to MBM. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for MBM no in vivo data for local genotoxicity are available. Furthermore from a mechanistic toxicological point of view the positive in vitro genotoxicity is most likely due to formaldehyde release, i.e. reflects the local genotoxicity of formaldehyde and MBM.

It is true that the genotoxicity classification should primarily be based on the consideration of potential effects in the germ cells, which is explained in chapter 4.8.6. and 4.8.7. of the CLH report. However as explained in chapter 4.8.4 of the CLH report the RAC opinion proposing classification of formaldehyde (from 2012) supported that "due to the induction of genotoxic effects in vivo on somatic cells at site of contact, which are supported by positive findings from mutagenicity and genotoxicity tests in vitro, … classification of formaldehyde for mutagenicity category 2 in accordance with the CLP Regulation, with the hazard statement H341 (Suspected of causing genetic defects) is therefore warranted..." The RAC opinion, referring to the ECHA CLP guidance section 3.5.2.1.2. and 3.5.1., explains that positive in vitro genotoxicity data plus positive in vivo (systemic and/or local) somatic genotoxicity data may support category 2 classification for mutagenicity. Since formaldehyde data were read across to MBM also this harmonized conclusion was suggested for MBM.

Formaldehyde and MBM is considered a local carcinogen. In the presence of a clear biocidal mode of action and knowledge of equilibrium behaviour, hydrolysis and reaction kinetics negative SARs should be disregarded.

Last 3 paragraphs:
Ad 1: The available hydrolysis data just indicate that highly concentrated MBM is relatively

stable in water and with higher aqueous dilutions MBM hydrolyses to formaldehyde and morpholine (DT50 about 2.4 hours). Further data indicate long stability of the formaldehyde releaser in metal working fluid. However these data do not mirror formaldehyde reactivity and release upon contact with biological tissue.There are no data informing on the exact kinetics of formaldehyde release from contact with biological material.
Classification relates to the intrinsic property of a substance, the in use concentrations are of very limited relevance. Moreover also the new exposure data referenced in the comment demonstrate obviously the release and presence of formaldehyde at sites due to the hydrolysis of MBM. Choice of operational conditions and risk management measures are important parameters for keeping release of formaldehyde at a low level and can result in higher levels, if they are not optimized. Referring to the provided data, it is acknowledged, that mwf-solution might release more slowly and lower amounts of formaldehyde than solutions containing aqueous formaldehyde only. Nevertheless, referring also to the referenced data, formation of formaldehyde cannot be disregarded for the indended use and occurs at relevant levels requiring adaption of operational conditions and risk management measures. The actual Biocides draft CAR indicates an acceptable risk for human health for the intended uses described in the Biocides draft CAR.

Ad2: As mentioned above (ad 1) classification relates to the intrinsic property of a substance; moreover choice of operational conditions and risk management measures are important parameters for keeping release of formaldehyde at a low level and can result in higher levels, if they are not optimized.

Ad3: With regard to potential exposure considerations please see above (ad1, ad2). With regard to the available carcinogenicity data please take into consideration that in the sub-chronic study and in the developmental toxicity study with MBM local effects in the gastrointestinal tract were observed. In principle such effects can develop into tumours upon long term exposure. A genotoxic mode of action contribution cannot be excluded; the negative or ambiguous in vivo genotoxicity data do not provide support for systemic genotoxicity, but they do not allow a conclusion for the presence or absence of potential local genotoxicity. The available genotoxicity data for MBM are consistent with the available data for formaldehyde: The data were positive in vitro and negative or ambiguous for systemic genotoxicity in vivo. This similarity supports the read across of the formaldehyde data to MBM. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for MBM no in vivo data for local genotoxicity are available. Furthermore from a mechanistic toxicological point of view the positive in vitro genotoxicity is most likely due to formaldehyde release, i.e. reflects the local genotoxicity of formaldehyde and MBM. However for formaldehyde respiratory exposure was observed as the critical route for local tumour development. Respiratory toxicity studies with MBM were neither available nor required. We acknowledge the RAC conclusion that the carcinogenicity of formaldehyde is related to local effects.

RAC's response
No further comment.

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	8
Comment received				
The NL CA agrees with the classification for Carc. 1B (H350) for 4-(morpholin-4-ylmethyl)morpholine (MBM) based on the read-across from human epidemiology studies and animal carcinogenicity data available for the hydrolysis product formaldehyde.				

Formaldehyde has a harmonized classification as Carc. Cat 1B (EC 605/2014). The intratracheal instillation study summarized in paragraph 4.1.1.2 clearly shows that ~60% of the MBM was expired during the 7 day sampling period as formaldehyde and carbon dioxide. In aqueous solutions and biological systems, MBM hydrolyses to formaldehyde and morpholine (hydrolysis study, section 5.1.1.1, p. 47-48 CLH Report). This means that when the substance is provided to test animals or humans through the oral or inhalation route substantial amounts of formaldehyde will be released. According to paragraph 1.5 (2) of Annex XI of REACH, grouping and read-across is justified if there is similarity based on common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals. In this case studies show that formaldehyde is generated from the hydrolysis. Therefore it is reasonable to assume that MBM will also induce local tumors although the location after inhalation may differ due to the differences in physical properties because formaldehyde is a gas whereas MBM is a liquid.
Dossier Submitter's Response
We acknowledge the support.
RAC's response
Considered in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	9
Comment received				
The proposed classification of MBM as Carc. 1B, H350 according to the releasable formaldehyde is supported. MBM is a labile formaldehyde precursor and hydrolyses completely in contact with biological tissues and fluids to formaldehyde. Therefore, local genotoxic effects and carcinogenicity are expected. MBM was also confirmed to be genotoxic in vitro.				
Dossier Submitter's Response				
We acknowledge the support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Finland		MemberState	10
Comment received				
With regard to carcinogenicity, the genotoxicity data of MBM supports the idea that due to release of formaldehyde, MBM is local genotoxic carcinogen. Thus, classification of Carc 1B for MBM based on read across from formaldehyde classification seems warranted. We acknowledge that classification of MBM to both Muta 2 and Carc 1B would be in line with RAC´s previous decision to classify formaldehyde to both hazard classes. However, we think that RAC should further consider whether classification of local genotoxic carcinogens to both mutagenicity 2 and carcinogenicity is adequate and necessary.				
Dossier Submitter's Response				
We acknowledge the support and in line with the CLH Dossier, chapter 4.8.7 we agree that the question should be further considered, if classifying for Muta 2 on the basis of local genotoxicity is adequate and necessary.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany	Lubrizol Deutschland	Company-Manufacturer	11

Comment received

See attached paper for additional information. In accordance with EU CLP (Regulation (EC) No. 1272/2008) classification of MBM is not required for genotoxicity based on the absence of genotoxicity in vivo. The mutagenic potential of MBM has been evaluated using a number of in vitro assays. MBM is weakly mutagenic in the presence of metabolic activation in Salmonella typhimurium strain TA100 and is positive with and without metabolic activation in the chromosome aberration assay with CHL cells and in the mouse lymphoma assay. In vivo studies, however, indicate that it is not genotoxic. MBM did not induce a significant increase in micronuclei in the in vivo mouse micronucleus assay and did not induce DNA synthesis in the liver from rats given orally administered doses up to 900 mg/kg. In accordance with the CLP guidance, the results from the in vivo assays on MBM in the form that it is placed on the market should be more heavily weighted as an indicator of the inherent genotoxic properties of MBM than the in vitro assays. Information presented elsewhere in this paper provide sufficient reasons why it is not scientifically credible to rely on data generated from experiments involving MBM at very low concentrations in an aqueous medium to define the inherent hazard character of this substance by consideration of the hydrolysis by-products.

Additionally, under CLP classification as a Mutagen is only required where there are demonstrated adverse effects on germ cells (i.e. inducing hereditable changes), or where hereditary effects can be predicted from effects on somatic cells. The hypothesis supporting the proposed classification of MBM as a mutagen, namely the hydrolytic release of sufficient 'bound' formaldehyde leading to 'free' formaldehyde at the site of contact means that the proposed classification is neither scientifically credible nor defensible. Numerous studies and RAC's own previous opinion on formaldehyde accept that formaldehyde has no significant toxicological effect distant to the site of exposure (RAC 2012). The absence of a credible mechanism for systemic distribution supports the conclusion that a worker's germ cells would never be exposed to sufficient formaldehyde released from MBM, and so the proposed classification of MBM as a mutagen is both disproportionate and not scientifically defensible.

ECHA comment: The following non-confidential attachment was provided with this comment. See also comments 2, 7 and 18 [see Attachment 2 and 3]

- *Harmonised classification and labeling proposal for N,N'-methylene bismorpholine (MBM) - Lubrizol comments for the public consultation*
- *Occupational Exposure to Formaldehyde from Metalworking Fluids Containing the Antimicrobial Agent Methylenebismorpholine*

The following confidential attachment was provided with this comment. See also comments 2, 7 and 18 [see Attachment 1 – confidential section]

- *TRW study report.pdf*

Dossier Submitter's Response

Please see our response to comment 2 and 10. For completeness the respective considerations are repeated here:

As shown in table 4.8-3 and 4.8-4 in the CLH report with regard to mutagenicity the available data for MBM are consistent with the available data for formaldehyde: The data

were positive in vitro and negative or ambiguous for systemic genotoxicity in vivo. This similarity supports the read across of the formaldehyde data to MBM. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for MBM no in vivo data for local genotoxicity are available. Furthermore from a mechanistic toxicological point of view the positive in vitro genotoxicity is most likely due to formaldehyde release, i.e. reflects the local genotoxicity of formaldehyde and MBM.

It is true that the genotoxicity classification should primarily be based on the consideration of potential effects in the germ cells, which is explained in chapter 4.8.6. and 4.8.7. of the CLH report. However as explained in chapter 4.8.4 of the CLH report the RAC opinion proposing classification of formaldehyde (from 2012) supported that "due to the induction of genotoxic effects in vivo on somatic cells at site of contact, which are supported by positive findings from mutagenicity and genotoxicity tests in vitro, … classification of formaldehyde for mutagenicity category 2 in accordance with the CLP Regulation, with the hazard statement H341 (Suspected of causing genetic defects) is therefore warranted..." The RAC opinion, referring to the ECHA CLP guidance section 3.5.2.1.2. and 3.5.1., explains that positive in vitro genotoxicity data plus positive in vivo (systemic and/or local) somatic genotoxicity data may support category 2 classification for mutagenicity. Since formaldehyde data were read across to MBM also this harmonized conclusion was suggested for MBM.

RAC's response

According to the Guidance to Regulation (EC) No 1272/2008 on CLP, hazard classification for germ cell mutagenicity primarily aims to identify substances causing heritable mutations in germ cells or being suspected of causing heritable mutations due to the induction of genotoxic effects in soma cells in vivo. This applies for substances with a sufficient systemic availability. In addition, information is given whether it is possible that genotoxic effects may play a role at carcinogenesis. Therefore the guidance also regulates the in vivo testing as well as a possible classification of substances that can act only locally at site of contact due to their low systemic availability.

MBM has a low systemic availability due to its hydrolysis. Accordingly the available in vivo results are of low relevance because they examine a possible of mutagenic effect in distance to the site of exposure. Therefore their results do not allow the conclusion that the substance is not genotoxic in the whole animal. There is no test with MBM which assessed whether genotoxic effects will be induced in cells at site of first contact . But for the evaluation of toxicological properties of MBM is taken into account that its hydrolysis product formaldehyde is already classified as Category 2 mutagen due to the induction of local genotxic effects.

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	12

Comment received

The NL CA agrees with the classification for Muta 2 (H341) because of the positive results in in vitro genotoxicity tests (Ames, chromosomal aberrations test and mouse lymphoma assay [Table 4.8-1, p. 36, CLH Report]). It is considered that the genotoxicity of MBM is related to the hydrolysis product formaldehyde which has an Annex VI classification of Muta. 2.

Dossier Submitter's Response

We acknowledge the support. Please see also our response to comment 10.

RAC's response

RAC takes note of the support.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Finland		MemberState	13
Comment received				
We acknowledge that the proposed classification of mutagenicity category 2 for MBM is justified by positive in vitro results on mutagenic activity of MBM, mechanistic considerations of total releasable amount of formaldehyde in contact with biological media, and read across from mutagenic properties of formaldehyde. We also note that this classification is in line with CLP guidance 2013 (3.5.1., page 379), stating that local genotoxicants which are incapable of causing heritable mutations because they cannot reach the germ cells, can be classified in category 2. This provides indication that substance may be carcinogenic.				
Dossier Submitter's Response				
We acknowledge the support. Please see also our response to comment 10.				
RAC's response				
RAC takes note of the support.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	14
Comment received				
The NL CA agrees for no classification for reproductive toxicity.				
Dossier Submitter's Response				
We acknowledge the support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	15
Comment received				
Classifications Acute Tox. is not covered by the classification Skin Corr 1B, H314. Please add the missing classifications. If no data are available with MBM, please refer to formaldehyde classification as you did for the other endpoints. 4.2.1.4 Acute toxicity – products of hydrolysis, formaldehyde (p.27): Please correct the harmonised classification of formaldehyde.				
Dossier Submitter's Response				
<u>MBM:</u> We are aware that actual practice for classification of corrosive substances with regard to actue toxicity depends on the question, if experimental data for acute toxicity are available or not. However this results in an inconsistent classification approach, even within the group of formaldehyde releasers. Furthermore please acknowledge that LD50 and LC50 estimates from acute toxicity studies may depend on the concentration in which the corrosive				

substance is applied (orally and dermally but also in respiratory studies the concentration in the aqueous aerosol). Testing the same substance at different concentrations may lead to different LD50 or LC50 estimates or classification conclusions. Formaldehyde –releasers may be an exception to this, in that the total releasable formaldehyde may more important than the concentration. However please also consider that the OECD test guidelines are explicit on the fact that substances should not be tested at corrosive concentrations. This could not provide any new toxicological information. Consequently in a situation where we can be reasonably sure that severe local effects would be the cause for acute toxicity - it is in our view not appropriate to classify for acute toxicity. <u>Formaldehyde:</u> We agree that the CLH Dossier can be amended with the harmonized classification, though it seems that acute toxicity classification was not evaluated by RAC.
RAC's response
The Rapp agree with the proposal of the FR CA.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	16
Comment received				
Subcategorisation as Skin Corr. 1B is not supported, we propose to assign skin corrosive Category 1 without specifying a subcategory. Reason: according section 3.2.2.4 of the CLP-Guidance "Decision on classification. Where the substance is classified as a skin corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the substance should be assigned skin corrosive Category 1." This is also referred to in the CLH report section 4.4.1.6 ("The data demonstrate corrosive potential but do not allow differentiating between sub-categories, since only a 4 hour exposure was applied.")				
Dossier Submitter's Response				
Though this will change in future, according to the actual legal text of the CLP Regulation subcategorization is required. Consequently Skin Corr Cat. 1B is proposed based on the following arguments: Based on the old system the substance causes burns and warrants the classification with C, R34 (in the old system no sub-categorisation analogous to categories 1B/1C is foreseen). Annex VII of the CLP Regulation suggests to translate category C, R34 to Skin Corr. Cat 1B. Furthermore the MBM hydrolysis product formaldehyde is classified in Category 1B.				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	17
Comment received				
1.3 Proposed harmonised classification; 3.3 Serious eye damage/eye irritation (p.9): Please correct the "conclusive but not sufficient for classification" to Skin Corr 1B.				
Dossier Submitter's Response				
We suggest to change the entry to n.a. (not applicable), since the substance is classified for				

skin corrosion already.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany	Lubrizol Deutschland	Company-Manufacturer	18
Comment received				
See attached paper for additional information. In accordance with EU CLP (Regulation (EC) No. 1272/2008), there is no credible, scientific justification for classifying MBM as a skin sensitiser based on the information presented in the dossier. The skin sensitization test (guinea pig maximization) was considered inconclusive by the evaluating Competent Authority because the 10% topical induction concentration did not cause any irritation. However, rejection of this scientifically-valid sensitisation study in favour of extrapolation to a hypothesis of instantaneous release of sufficient 'bound' formaldehyde to cause an adverse effect following dermal exposure is unjustified. As hapten formation and distribution to the lymph through systemic circulation is required to elicit the sensitisation effect, the conclusion that there is no credible mechanism that would facilitate translocation from the site of exposure to systemic circulation (NRC 2011) is supportive of no classification for sensitisation. Further, from the experimental perspective, the aforementioned assay was conducted using a non-aqueous vehicle to evaluate the sensitisation profile of the MBM molecule to support a conclusion of intrinsic toxicity. Given the recognised confounding factor associated with the known sensitisation potential of formaldehyde and the anticipated high rate of hydrolysis of MBM at the low concentrations predicted to be needed during the experiment because of the known corrosive nature of MBM the conclusion that MBM is inherently sensitising is unfounded. The criticism of the study and the reason for the findings being considered equivocal by the evaluating Competent Authority was the lack of irritation seen during the induction phase of the main study at the dose levels selected. Using a higher intradermal and induction concentration than tested in the main study was not possible due to MBM's inherent corrosivity and concerns for animal welfare (i.e. severe lesions (necrosis) were observed for several animals during the sighting assay). Despite the equivocal outcome of this study experimental data should not be superseded by the unproven hypothesis of an immediate release of sufficient 'bound' formaldehyde upon dermal contact and transfer across the skin barrier in sufficient amounts to cause a cellular reaction. Toxicokinetic measurements using radio-labelled material showed that the highest amount of radioactivity was retained in the stratum corneum with formaldehyde reacting with macromolecules mostly at the outer layers of the skin thus limiting further penetration and systemic distribution. From these experiments it must be inferred that insufficient released formaldehyde would penetrate into the epidermis to induce sensitisation following dermal exposure to MBM under normally expected use conditions. It follows therefore that there is no convincing evidence that dermal sensitisation is an intrinsic property of the MBM molecule. Instead classification considerations for sensitisation should be based on the amount of free (unbound) formaldehyde present when MBM is placed on the market rather than being based on a consideration of the amount of 'releasable' formaldehyde that may occur under uncertain experimental conditions. The stability study shown in Table 1 demonstrates that release of formaldehyde by hydrolysis is not expected to occur at higher concentrations even in the presence of moisture and the actual release kinetics of MBM in the form that it can reasonably be expected to be used do not support the hypothesis presented in this dossier to justify classification of MBM as a skin sensitiser. *ECHA comment: The following <u>non-confidential</u> attachment was provided with this*				

comment. See also comments 2, 7 and 11 [see Attachment 2 and 3]

- *Harmonised classification and labeling proposal for N,N'-methylene bismorpholine (MBM) - Lubrizol comments for the public consultation*
- *Occupational Exposure to Formaldehyde from Metalworking Fluids Containing the Antimicrobial Agent Methylenebismorpholine*

The following confidential attachment was provided with this comment. See also comments 2, 7 and 11 [see Attachment 1 – confidential section]

- *TRW study report.pdf*

Dossier Submitter's Response

Please see our response to comment 2. For completeness the respective consideration is repeated here:

The skin sensitization study (GPMT) with MBM was negative, but the conclusion was not reliable since no skin irritation was observed with the topical induction with 10% solution in Alembicol D. The pretest-data indicates that the concentration-response relationship for skin irritation to corrosion seems to be steep (1/6 animals showed slight erythema with 1% as well as with 5% topical application; 4/6 animals showing slight erythema with 10% topical application, 4/6 animals showing necrosis with 20% topical application). Formaldehyde reaction with proteins is a local event, translocation of the modified protein to systemic circulation may be subsequent. From the dermal absorption study summarized in the CLH report a 60% to 70% dermal absorption rate was concluded. Details of the study summaries are presented in the Annex to the CLH report. RAC may develop its own opinion how to weight the negative skin sensitization results of the GPMT test of MBM in the context of an overall WoE including knowledge of formaldehyde release at site of contact with biological tissues.

RAC's response

It is debatable whether the GPMT should be considered as negative since 3/20 animals responded at the very low induction concentration.

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	19

Comment received

The NL CA agrees with the classification for Skin Sens. 1 (H317) based on read-across data from formaldehyde which has an Annex VI harmonized classification of Skin Sens. 1 (H317). There is sufficient evidence that formaldehyde is a hydrolysis product of MBM where it has been estimated that for each mg of MBM, 0.23 mg of formaldehyde is generated. We suggest not to apply a SCL for skin sensitisation as the rate of hydrolysis of MBM to formaldehyde may affect the potency. In addition, the proposed SCL of 1.2% is comparable to the GCL of 1% for Skin Sens. 1.

Skin Corrosion
The Netherlands disagrees with classification for Skin Corr. 1B (H314) and proposes Skin Corr. 1 (H314) based on corrosive properties of the hydrolysis product formaldehyde and the irreversible skin damage observed for MBM (pg. 29 CLH Report). There is insufficient data for sub-classification.

In our opinion classification for serious eye damage (Cat. 1) is required but no labelling as explained in the CLP guidance chapter 3.3.2.4.

The Netherlands does not agree that in general corrosive substances should not be classified for acute toxicity, STOT SE and STOT RE because;
• This is not in line with the legal criteria
• This is not in line with the current RAC approach
In addition EUH071 should be considered.

Therefore, according to the data provided in Section 4.2 (p.27-28 in CLH Report) and comparison criteria in Section 4.2.4 (p. 28 in CLH Report), Acute Tox. 4 (H302) and Acute Tox. 4 (H312) are warranted. Read across for acute inhalation toxicity from formaldehyde to MBM based on the formation of 6.1 times less formaldehyde is considered not justified because formaldehyde is a vapour and MBM a liquid resulting in different deposition sites within the respiratory tract and therefore likely quantitative and qualitative (site and affected surface) differences. Read-across for acute dermal toxicity is supported as this effect is most likely related to the local corrosivity which has been shown also for MBM.

The Netherlands agrees that no classification for STOT SE 3 (H335) is required given that no other specific target toxicities are expected than the respiratory irritation. According to Section 3.8.2.5 of CLP, 'Classification as acutely toxic and/or corrosive is considered to cover and communicate specific toxicological effect(s) adequately' and 'It is reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion'. The additional labelling with EUH071 would also warn the user of the effects on the respiratory tract.

With regards to STOT RE, according to Section 3.9.2.5.1 of CLP, 'if the dose is more than half an order magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity'. For acute toxicity, 500 < LD50 < 2000 mg/kg bw (rat). In a 14-day study, thickening of the non-glandular stomach was observed at 50 mg/kg bw. In a 90-day study, the LOAEL for local effects in the stomach (thickening of the non-glandular part) was 50 mg/kg bw and the NOAEL was 15 mg/kg bw (p. 33, CLH Report). At 50 mg/kg bw, lesions in the nasopharyngeal epithelium and the non-glandular stomach were found in males; in females only lesions of the non-glandular stomach (acanthosis and hyperkeratosis) were detected. In addition, one rat in the 50 mg/kg bw died during the exposure period and showed epithelial sloughing of the glandular gastric epithelium. Given that local stomach effects were reported at 50 mg/kg bw (more than a half an order of magnitude lower than the acute toxicity), then STOT RE 2 (H373) is warranted.
Also the additional label EUH029: "Contact with water liberates toxic gas" should be considered as formaldehyde is formed and released which is classified with Acute Tox. 2 H330.

Dossier Submitter's Response

<u>Skin sensitization</u>
In line with an earlier discussion at the BPC WG we agree to delete the SCL and suggest the GCL for MBM.

<u>Skin corrosion</u>
Though this will change in future, according to the actual legal text of the CLP Regulation subcategorization for skin corrosion is required. Consequently Skin Corr Cat. 1B is proposed based on the following arguments: Based on the old system the substance causes burns and warrants the classification with C, R34 (in the old system no sub-categorisation analogous to categories 1B/1C is foreseen). Annex VII of the CLP Regulation suggests to

translate category C, R34 to Skin Corr. Cat 1B. Furthermore the MBM hydrolysis product formaldehyde is classified in Category 1B.

Eye damage
We respect the text in the CLP guidance and the view of the CA NL. However we do not understand it, the Hazard Statement is part of the classification and already mentions the eye damage. It also does not seem to be practice yet – the CLP regulation does not contain classification entries of Eye damage in addition to skin corrosion?

Acute toxicity:
We are aware that actual practice for classification of corrosive substances with regard to actue toxicity depends on the question, if experimental data for acute toxicity are available or not. However this results in an inconsistent classification approach, even within the group of formaldehyde releasers. Furthermore please acknowledge that LD50 and LC50 estimates from acute toxicity studies may depend on the concentration in which the corrosive substance is applied (orally and dermally but also in respiratory studies the concentration in the aqueous aerosol). Testing the same substance at different concentrations may lead to different LD50 or LC50 estimates or classification conclusions. Formaldehyde –releasers may be an exception to this, in that the total releasable formaldehyde may more important than the concentration. However please also consider that the OECD test guidelines are explicit on the fact that substances should not be tested at corrosive concentrations. This could not provide any new toxicological information.
Consequently in a situation where we can be reasonably sure that severe local effects would be the cause for acute toxicity - it is in our view not appropriate to classify for acute toxicity.

STOT SE 3: We acknowledge the support for non-classification. We do not have an objection to an additional label with EUH071(Corrosive to the respiratory tract), though it may be considered an over-labelling.

STOT RE: According to CLP Regulation, Annex I, Article 3.9.1.1. we do not suggest to classify for STOT RE. In our view the principal effect appears to be corrosion/irritation, which is already covered by classification for Skin Corr. 1 (H314).

EUH029 (Contact with water liberates toxic gas): We do not have objections to this proposal.

RAC's response

The Rapp's view is that there is uncertainty about the nature and severity of the gastrointestinal lesion and find it uncertain to conclude that these were the cause of death noting that other serious general health conditions were observed. The report summary itselt stated 'Rats which died during post exposure observation period revealed varying degree of mucosal lesions in the gastro-intestinal tract (stomach and intestine). No effects were detected in survivors.'

The NL CA's view is agreed on, classification on corrosion does not cover classification on acute toxicity (for all routes). With regards to the classification on eye damage, see previous decisions on other formaldehyde releasers.

Other points were considered for the opinion document.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	20

Comment received
The proposed classification of Skin Sens. 1, H317 is supported. It is proposed not to assign a SCL. In the interest of reduction of animal use and suffering, read-across to formaldehyde is accepted. However, the extrapolation based on MW neglects the substance specific properties (e.g. due to lower reactivity MBM might reach deeper dermal layers). Thus, in absence of substance specific data the specific concentration limit (SCL) of 1.2% cannot be supported. SCL above the GCL may only be set in exceptional circumstances, if scientific information is adequate, reliable and conclusive for that particular skin sensitiser. Such data are not available for MBM. The GCL of 1% is proposed.
Dossier Submitter's Response
In line with an earlier discussion at the BPC WG we agree to delete the SCL and suggest the GCL for MBM.
RAC's response
The proposal/view is supported.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	21
Comment received				
Classifications STOT SE is not covered by the classification Skin Corr 1B, H314. Please add the missing classifications. If no data are available with MBM, please refer to formaldehyde classification as you did for the other endpoints.				
Dossier Submitter's Response				
Please see comment 19 and our response to this.				
RAC's response				
In general agreed with FR CA, in this case no classification as STOT SE is proposed.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	22
Comment received				
Classifications STOT RE is not covered by the classification Skin Corr 1B, H314. Please add the missing classifications. If no data are available with MBM, please refer to formaldehyde classification as you did for the other endpoints.				
Dossier Submitter's Response				
Please see our response to comment 19.				
RAC's response				
The proposal is considered in the opinion.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	United Kingdom		MemberState	23
Comment received				

The proposal considers MBM rapidly degradable. Therefore, ecotoxicity data for its degradants are considered in the CLH report. We note that Table 5.3.2.1-3 (Growth inhibition of formaldehyde on Algal [Reference study Eisenträger,2003]) does not include data for the NOErC endpoint. Is this data available or can an ErC10 be calculated?
Dossier Submitter's Response
This data is not available, and an ErC10 can not be calculated, since the algae data stems from published literature. Please see DOC_III-A7.4.1.3_HCHO.doc (attached to the CLH-report) which summarises the available data. This DOC IIIA was evaluated by the DE competent authority when establishing the DOC IIA of the Formaldehyde core dossier.
RAC's response
Noted

ATTACHMENTS RECEIVED

1. Statement supporting the comments provided by [name of FABI member]concerning the proposed harmonised classification for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)(MBO). *Submitted on 22.01.2015 by Verband Schmierstoff-Industrie e.V. (Filename: FABI statement on harmonised classification proposal - draft collated co .docx) (Please refer to comment 5)*

2. Harmonised classification and labeling proposal for N,N'-methylene bismorpholine (MBM) - Lubrizol comments for the public consultation. *Submitted by Lubrizol Deutschland on 23.01.2015. (Filename: MBM comments for public consultation - Dec2014finalsubmitted version - 23Jan2015.docx) (Please refer to comments 2, 7, 11 and 18)*

3. Occupational Exposure to Formaldehyde from Metalworking Fluids Containing the Antimicrobial Agent Methylenebismorpholine. *Submitted by Lubrizol Deutschland. (Filename: Formaldehyde occupational study - non-confidential version). (Please refer to comments 2, 7, 11 and 18)*

4. Legal & Regulatory Statement from FABI members in response to the 45 day public consultation on the proposed harmonised classification of N ,N'-methylenebismorpholine *(Filename: FABI - Legal and regulatory statement on the proposal for harmonised classification of MBM) (MBM). Submitted by FABI - Formaldehyde Biocides Interest Group on 23.01.2015 (Please refere to comment 6)*

5. Statement supporting the comments provided by Lubrizol concerning the proposed harmonised classification for N,N'-methylenebismorpholine (MBM) *(Filename: FABI - Statement on the proposal for harmonised classification of MBM). Submitted by FABI - Formaldehyde Biocides Interest Group on 23.01.2015 (Please refer to comment 6)*

CONFIDENTIAL ATTACHMENTS RECEIVED

1. TRW study report.pdf. *Submitted by Lubrizol Deutschland on 23.01.2015. (Please refer to comments 2, 7, 11 and 18)*

Attachments added by Dossier Submitter AT

1. Carcinogenicity of MBM, Justification for non-submission of data (Filename: Doc III A6_7 MBM non sub.doc) *[Please refer to comment 2]*