Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2); [MBO]

EC Number: -
CAS Number: -

CLH-O-0000001412-86-95/F

Adopted

4 December 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE AND 2-HYDROXYPROPYLAMINE (RATIO 3:2); [MBO]

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.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2); [MBO]
CAS number: -
EC number: -
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 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 formaldehyde. As part of a classification dossier, we have no comments regarding environmental hazard. Nevertheless, a new algae study might be requested in an evaluation dossier.				
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" (see attached document DOC_I_LOEP_HCHO_core.pdf). We hope that this approach is satisfactory for the needs of the RAC.				
RAC's response				
The views of FR CA are noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	2
Comment received				
1. In aqueous solutions MBO is intended to hydrolyse to formaldehyde and 2-hydroxypropylamine. It is considered likely that the toxicity or toxicological potency of MBO is due to its hydrolysis product formaldehyde. The classification as proposed by the dossier				

submitter is, in general, supported. Classification as Skin Corr. 1 would be preferred over sub-categorisation as Skin Corr. 1B as explained below.

2. Concerning the proposed labelling (Precautionary statements) we like to remark that along with 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

1. 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 hydrolysis product formaldehyde is classified in Category 1B.
2.OK, we will change the P statements as proposed by DE.

RAC's response

Noted.

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

Comment received

This paper is send to RAC in behalf of two companies Lubrizol Limited and Schülke & Mayr GmbH. Please note that this paper was done in collaboration of these two parties.

Contact Lubrizol:
Mick Wragg
mick.wragg@lubrizol.com

ECHA comment: The following non-confidential attachments were provided with this comment. Please also refer to Comments 8 and 11[Attachments 1 – 7]

- Formaldehyde releasers: principles of chemistry and hydrolysis. A. Bitsch. Presentation, FABI Information Day 9th of December 2014, Vienna
- The situation of formaldehyde releasers and the need for a holistic approach on in-can preservatives (PT 6), Didier Leroy, FABI Information Day 9th of December 2014, Vienna
- The Use of Formaldehyde Releasing Biocides and Chemicals in the Oil and Gas Industry. H. Craddock. Presentation, 12.12.2014
- Typical uses and benefits of formaldehyde releasers as metalworking-fluid preservatives. 4. S. Baumgartel.Presentation, 12.12.2014
- Statement from FABI members in response to the public consultation on potential candidates for substitution for MBM. 10.04.2014
- Harmonised classification and labeling proposal for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)(MBO) comments for the public consultation from companies Lubrizol and Schülke
- Short Summaries of Studies

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE AND 2-HYDROXYPROPYLAMINE (RATIO 3:2); [MBO]

ECHA comment: The following confidential attachments were provided with this comment.Please also refer to Comments 8 and 11

- MBO comments for public consultation - 23 01 2015 draft
- Concentration of formaldehyde in ambient air byaddition of ”grotamar 71” into diesel fuel tanks
- Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO“ or „Grotan OX, Schülke und Mayr“
- Formaldehydemeasurements in the ambient air of a production facility by the use of ”Grotan OX, Schülke und Mayr“
- Study Report – Cooling lubricants – test on free formaldehyde
- Study Report – Diesel additives – test on free formaldehyde
- Study Report – MBO vs Formalin – test on identity and differences
- Study report – Diverse test items – test on free formaldehyde

Dossier Submitter’s Response

The physical form of MBO (further described as reaction product, RP 3:2) was respected for the assessment: RP 3:2 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 MBO is estimated to be above 1 Pascal, respiratory exposure scenarios considering this are presented in the draft Biocides Competant Authority Report (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 indicate that formaldehyde is released from the concentrated product as well as from the in use solutions in relevant concentrations. The measurements are intended to represent realistic use conditions. Risk management measures like Local Exhaust Ventilation (LEV) and funnels are required to keep the formaldehyde concentrations low or below the detection limit. The potential for release of formaldehyde is demonstrated. Non-acceptable formaldehyde concentrations in air are likely, if no risk management measures are applied in this case. Nevertheless, 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 RP 3:2 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 additionthe RAC classification for formaldehyde is based on limited evidence in humans and sufficient evidence in animal studies. No experimental carcinogenicity data are available for RP 3:2, consequently these were read across from formaldehyde, based on mechanistic toxicological considerations

Chapter 2.2. of the draft CLH report explains: ”No carcinogenicity study is available for the

substance, but hydrolyses to formaldehyde by dilution and by reaction with biological media is the mode of biocidal action. Hydrolysis studies indicate a DT50 of < 1 hour. It is proposed to read across the classification of formaldehyde to the formaldehyde-releaser based on consideration of total releasable formaldehyde."Instantaneous release of formaldehyde from the releaser upon contact with water was not 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 formaldehyde present in the reaction mixture will react with the biological material and the equilibrium mixture (reaction product 3:2) will shift towards new release of formaldehyde. This is also the principle of the biocidal activity. In fact also the skin corrosion studies with the undiluted RP 3:2 as well as the skin sensitization studies with higher diluted RP 3:2 document the biological reactivity of the formaldehyde releaser. The available hydrolysis data just indicate that highly concentrated RP 3:2 is relatively stable in water and with higher aqueous dilutions RP 3:2 hydrolyses to formaldehyde and 2-hydroxyl-propylamin quickly (DT50 below 1 hour). 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. 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 the RP 3:2, 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 RP 3:2 (see attached document Doc III A6.7 justif nonsub carcinogenicity.dox). 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 RP 3:2 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.

In the sub-chronic studies with RP 3:2 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 RP 3:2 were neither available nor required.

It is not appropriate to consider the final in use concentration of RP 3:2 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 formaldehyde in the higher dilutions of RP 3:2 in the end use fluids and the resulting exposure concentrations in air are considered and from immanent importance for the risk characterisation of the substance.

As shown in table 4.8-3 and 4.8-6 in the CLH report with regard to mutagenicity the available data for RP 3:2 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 RP 3:2. For Formaldehyde

positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for RP 3:2 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 RP 3:2.

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 4.8.3. and 4.8.4. 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 RP 3:2 also this harmonized conclusion was suggested for RP 3:2.

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.

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

RAC fully supports the DS's views.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany	UNITI Bundesverband mittelständischer Mineralölunternehmen e.V.	Industry or trade association	4

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE AND 2-HYDROXYPROPYLAMINE (RATIO 3:2); [MBO]

Comment received
We comment the proposed harmonised classification on Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) (MBO) with a brief attached UNITI statement to support the attached detailed statement of the Formaldehyde Biocide Interest Group (FABI) regarding the proposed harmonised classification of MBO as Carc. 1B, H350 and Muta 2, H341 in analogy to Formaldehyde. *ECHA comment: The following non-confidential attachments were provided with this comment [see Attachments 10 and 11]* - *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)* - *Statement of UNITI Bundesverband mittelständischer Mineralölunternehmen e.V. regarding the proposed harmonised classification and labelling of Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2), (MBO)*
Dossier Submitter's Response
The CLH regulation does not allow for socioeconomic considerations. With regard to the technical arguments for classification please see our response to comment No.3 However 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. This can and should be considered in the context of the biocides regulation. Legal statement of AT According to Annex I, Part 3.6.2.2.1, of the CLP Regulation 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. This provision refers solely to cancerogenicity and had to be applied by the Austrian eCA. Hence the classification of the proposed CLH Proposal focusses on the intrinsic property which results from the release and presence of formaldehyde, which leads to classification for Carc. Cat 1B referring to the available data. In addition, the evaluation of carcinogenicity performs on carcinogenicity data for the substance formaldehyde by using the "read across principle". 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.
RAC's response
RAC agrees with the statements of the DS. It should be noted that the MS CA's classification proposals are not based on the precautionary principle and RAC does not propose precautionary classifications. Classification is based on a weight of evidence from all relevant data - either taking into account reliable data on the substance of concern itself and/or using read across from other substances.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE AND 2-HYDROXYPROPYLAMINE (RATIO 3:2); [MBO]

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Belgium	FABI - Formaldehyde Biocides Interest Group	Industry or trade association	5

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. Reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) (MBO) 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 MBO could be by analogy applicable for all formaldehyde releasers.

ECHA comment: The following non-confidential attachments were provided with this comment [see Attachments 8 and 9]:

- Legal & Regulatory Statement from FABI members in response to the 45 day public consultation on the proposed harmonised classification of Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) (MBO)
- Statement supporting the comments provided by Schülke concerning the proposed harmonised classification for reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) (MBO)

Dossier Submitter's Response

Please see our response to comment No.3

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

FABI raised concerns that the CLH Report for MBO 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 MBO 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 MBO 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 MBO. 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 MBO 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 MBO 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 MBO and rejects the accusations made by FABI.
RAC's response
No new arguments were identified in the comment. Again the detailed response of the DS is acknowledged.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	6
Comment received				
The NL CA agrees with the classification for Carc. 1B (H350) for the reaction product (RP) of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) based on the read-across from human epidemiology studies and animal carcinogenicity data available for the hydrolysis product formaldehyde. Formaldehyde has a harmonised classification as Carc. Cat 1B (EC 605/2014). The hydrolysis study summarized in paragraph 5.1.1 clearly shows the substantial formation of formaldehyde when this substances is diluted in water. 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 the hydrolysis study shows that from RP 3:2, formaldehyde is formed. Therefore it is reasonable to assume that RP 3:2 will also induce local tumours although the location after inhalation may differ due to the differences in physical properties because formaldehyde is a gas whereas RP 3:2 is a liquid.				
Dossier Submitter's Response				
We acknowledge your support.				
RAC's response				
RAC takes note of the support.				

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	7
Comment received				
We support the proposed classification as Carc. 1B; H350. The presented data (Page 49, chapters 4.9.5, 4.9.6.) demonstrated that from the mechanistic point of view and with regard to the key events irritation and local mutagenicity, MBO can be regarded " equivalent" to formaldehyde, warranting read-across and classification as Carc. 1B. It is not clear, how the fixation to and release from hydroxypropylamine of formaldehyde will affect the carcinogenic potency. While fixation reduces the immediate free concentration of the carcinogen, it may also enhance				

penetration into the living tissue.

Dossier Submitter's Response

We agree that there is uncertainty related to the carcinogenic potency estimate for the formaldehyde releaser. The CLH Dossier Annex "doc IIA, human health effects assessment", chapter 3.11. and 3.12. contains a discussion of these uncertainties related to acceptable exposure level estimation.
In short we consider the uncertainties acceptable, since 1) only dominant local effects were observed in the repeated dose studies for RP 3:2 and 2) the in vivo tests for systemic genotoxicity are negative, which means most likely that the substance could not reach the target tissues, 3) molar read across of the systemic NOAEL from formaldehyde results in the LOAEL/NOAEL range of RP 3:2 and 4) the formaldehyde data critical for the risk assessment of local effects were derived from humans, new animal data for RP 3:2 would contain other uncertainties with regard to reliability and relevance including mixture behaviour at various concentrations, pH, temperature and formulation components.

RAC's response

See also comment 14. Classification for Skin Corrosion (Cat 1 B) has been adopted by RAC with a slightly different reasoning as proposed by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		Individual	8

Comment received

III. Carcinogenicity
The current classification proposal is not based on the concept that MBO is inherently a carcinogen but that human exposure liberates formaldehyde which is the carcinogenic component. Therefore the classification proposal is dependent on exposure factors which govern the liberation of formaldehyde. It is therefore essential that such exposure factors are reviewed to assess the degree of potential exposure, and are integral to the classification discussion.

In accordance with EU CLP Regulation we strongly suggest that classification is not required for carcinogenicity for MBO based on numerous lines of evidence presented below. Further, in view of the explanation of the hydrolytic stability of MBO in the form that it is placed on the market and the very slow rate of formaldehyde-release (as a proportion of total dosed MBO) during its use as intended (i.e. in end use diluted metalworking fluid) there is demonstrably no credible scientific justification for classifying MBO as a suspected carcinogen, either in terms of direct evidence or on a weight-of-evidence approach.
1) MBO as manufactured and in the form that is placed on the market contains less than 0.1% 'free' or 'unbound' formaldehyde as an impurity.
2) CLP states that "carcinogenic potential can be inferred from in vivo and in vitro …mutagenicity studies". In vivo studies demonstrate that MBO 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 alternative approaches for the substance such as QSAR and Read Across predictions can be used when a substance has not been tested for carcinogenicity. The OECD Toolbox version 3.2 was used to profile MBO and based on QSAR predictions for

carcinogenicity as well as read across predictions based on chemicals in the same category that have experimental data on carcinogenicity MBO was confirmed to be not classifiable.

On this basis MBO itself cannot be considered to be inherently carcinogenic following the classification guidance.
Read-across to formaldehyde has been demonstrated to be scientifically unsound because there is no credible evidence to suggest repeated exposure of workers to MBO would release sufficient formaldehyde to cause tumours. On this basis MBO itself cannot be considered to be inherently carcinogenic in accordance with the classification guidance.
1) The proposed classification of MBO for carcinogenicity relies solely on the carcinogenic effects of released formaldehyde and that sufficient amount of formaldehyde is released at the nasopharyngeal cell surface following chronic exposure to MBO. This is because numerous scientific articles and the previous RAC opinion for formaldehyde recognize that there is a threshold for critical effects and potential carcinogenicity of formaldehyde (e.g., at 2 ppm; RAC 2012). The conclusion that the occurrence of tumors is the result of chronic proliferative processes and that the genotoxicity of formaldehyde plays no or at most a minor part in its carcinogenic potential is summarized by Gelbke et al. The published literature also considers exogenous exposure to be insignificant compared to exposure to endogenous 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. (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 MBO 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 MBO/water solutions at very low dilutions. The measurements of "free" formaldehyde and workshop exposure data presented in this paper demonstrate that quantitative application of this data for use in the read-across is not appropriate. It should be noted that the RAC has 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). While this is not conclusive evidence of a threshold value, formaldehyde contact with biological tissue would need to be at a level sufficient to trigger an irritant (cytotoxic) and/or cell proliferative response in the nasopharyngeal epithelium to result in cancers. Being able to demonstrate this, or at least put forward a credible argument that it occurs, should be a necessary pre-requisite for classifying MBO as a carcinogen as it is widely accepted that an irritant/cytotoxic/or cell proliferation response in the nasopharyngeal epithelium is a necessary precursor to the development of local tumours in this tissue. The RAC opinion for formaldehyde (RAC 2012) confirms that there is no evidence for any systemic effect of formaldehyde distant to the site of exposure. As a consequence we consider that there are numerous flaws in the proposal to classify MBO as a carcinogen based on release of total ('bound') formaldehyde following contact with 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 MBO molecule occurs immediately upon contact with the nasopharyngeal epithelium and would release sufficient 'bound' formaldehyde to cause an irritation/cell proliferation response.
It could be shown Data that concentrated MBO shows only very slow hydrolysis. (Table 1). Furthermore, as concentrated MBO is demonstrably corrosive to dermal skin it is reasonable to conclude that occupational exposure of the nasopharyngeal epithelium to neat MBO would result in the destruction of the epithelial cells rather than a cytotoxic effect or

induction of cell proliferation. Similarly, inhalation exposure to low concentrations of MBO for example through aerosolisation of an end-use metalworking fluid containing MBO at the typical effective dose of 1500 ppm would be well below the calculated DNEL (0.25 µg/L air) for local irritant effects.

2. It is an unrealistic assumption that the nasal epithelium of metal workers will be exposed to sufficient MBO in the workplace.
MBO is non-volatile (calculated vapour pressure; 0.014 hPa at 25°C calculated for the main constituent MBO by using EPI suite (Section AIII 3.2 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 reasonably expected (intended) use due to the physical properties of the substance. Aerosolisation is not a credible route of exposure to neat MBO even during handling by workers when formulating a mixture. There is however the possibility of exposure to MBO for metal workers due to aerosolisation of an end-use fluid during high energy operations such as grinding, cutting or milling. Actual workplace measurements show this to be practically irrelevant in terms of delivering sufficient MBO to the workers' respiratory system however. Furthermore, this route of exposure (via high energy aerosolisation) consideration would not be appropriate for other approved uses of MBO (e.g. PT6).

3. It is an unrealistic assumption that workers' nasopharyngeal epithelium will be exposed to supra-irritating levels of formaldehyde released from MBO on repeated occasions.
The preponderance of evidence accumulated through numerous studies and repeated analysis of the extensive cohort of toxicology data indicated that formaldehyde causes localized nasopharyngeal tumours following repeated inhalation exposure resulting in 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 this would not happen even in the worst-case occupational environment under conditions of reasonably expected (intended) use. 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. Furthermore, 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 MBO. In the absence of any pre-neoplastic changes in these studies and in the absence of any genotoxic response in whole animals it is considered that there is a weight-of-evidence against classification of MBO as a carcinogen.

ECHA comment: The following <u>non-confidential</u> attachments were provided with this comment. Please also refer to Comments 3 and 11 [Attachments 1 – 7]

- Formaldehyde releasers: principles of chemistry and hydrolysis. A. Bitsch. Presentation, FABI Information Day 9th of December 2014, Vienna
- The situation of formaldehyde releasers and the need for a holistic approach on in-can preservatives (PT 6), Didier Leroy, FABI Information Day 9th of December 2014, Vienna
- The Use of Formaldehyde Releasing Biocides and Chemicals in the Oil and Gas Industry. H. Craddock. Presentation, 12.12.2014
- Typical uses and benefits of formaldehyde releasers as metalworking-fluid preservatives. 4. S. Baumgartel.Presentation, 12.12.2014
- Statement from FABI members in response to the public consultation on potential

candidates for substitution for MBM. 10.04.2014
- Harmonised classification and labeling proposal for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)(MBO) comments for the public consultation from companies Lubrizol and Schülke
- Short Summaries of Studies

ECHA comment: The following confidential attachments were provided with this comment.Please also refer to Comments 3 and 11

- MBO comments for public consultation - 23 01 2015 draft
- Concentration of formaldehyde in ambient air byaddition of ”grotamar 71” into diesel fuel tanks
- Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO“ or „Grotan OX, Schülke und Mayr“
- Formaldehydemeasurements in the ambient air of a production facility by the use of ”Grotan OX, Schülke und Mayr“
- Study Report – Cooling lubricants – test on free formaldehyde
- Study Report – Diesel additives – test on free formaldehyde
- Study Report – MBO vs Formalin – test on identity and differences

Study report – Diverse test items – test on free formaldehyde

Dossier Submitter’s Response

Please see our response to comment 3, which contains all considerations also with regard to this comment No 8.

Here the considerations relevant to this comment 8 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 MBO (further described as reaction product, RP 3:2) was respected for the assessment: RP 3:2 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 MBO is estimated to be above 1 Pascal, respiratory exposure scenarios considering this are presented in the draft Biocides Competant Authority Report (CAR).

Also the new exposure data referenced in the comment indicate that formaldehyde is released from the concentrated product as well as from the in use solutions in relevant concentrations. The measurements are intended to represent realistic use conditions. Risk management measures like Local Exhaust Ventilation (LEV) and funnels are required to keep the formaldehyde concentrations low or below the detection limit. The potential for release of formaldehyde is demonstrated. Non-acceptable formaldehyde concentrations in air are likely, if no risk management measures are applied in this case. Nevertheless, 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: ”No carcinogenicity study is available for the substance, but hydrolyses to formaldehyde by dilution and by reaction with biological media is the mode of biocidal action. Hydrolysis studies indicate a DT50 of < 1 hour. It is proposed to read across the classification of formaldehyde to the formaldehyde-releaser based on consideration of total releasable formaldehyde.”Instantaneous release of formaldehyde from the releaser upon contact with water was not 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 formaldehyde present in the reaction mixture will react with the biological material and the equilibrium mixture (reaction product 3:2) will shift towards new release of formaldehyde. This is also the principle of the biocidal activity. In fact also the skin corrosion studies with the undiluted RP 3:2 as well as the skin sensitization studies with higher diluted RP 3:2 document the biological reactivity of the formaldehyde releaser. The available hydrolysis data just indicate that highly concentrated RP 3:2 is relatively stable in water and with higher aqueous dilutions RP 3:2 hydrolyses to formaldehyde and 2-hydroxyl-propylamin quickly (DT50 below 1 hour). 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. 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 4.8-6 in the CLH report with regard to mutagenicity the available data for RP 3:2 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 RP 3:2. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for RP 3:2 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 RP 3:2.

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 4.8.3. and 4.8.4. 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 RP 3:2 also this harmonized conclusion was suggested for RP 3:2.

Formaldehyde and RP 3:2 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 RP 3:2 is relatively stable in water and with higher aqueous dilutions RP 3:2 hydrolyses to formaldehyde and 2-hydroxyl-propylamin quickly (DT50 below 1 hour). 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 indicate that formaldehyde is released from the concentrated product as well as from the in

use solutions in relevant concentrations. The measurements are intended to represent realistic use conditions. Risk management measures like Local Exhaust Ventilation (LEV) and funnels are required to keep the formaldehyde concentrations low or below the detection limit. The potential for release of formaldehyde is demonstrated. Non-acceptable formaldehyde concentrations in air are likely, if no risk management measures are applied in this case.

Ad2: As mentioned above (ad 1) classification relates to the intrinsic property of a substance; moreover the available exposure models and data (see draft Biocides CAR, doc IIB) indicate potential exposure that requires risk management measures.

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 studies with RP 3:2 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 RP 3:2 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 RP 3:2. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for RP 3:2 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 RP 3:2. However for formaldehyde respiratory exposure was observed as the critical route for local tumour development. Respiratory studies with RP 3:2 were neither available nor required. We acknowledge the RAC conclusion that the carcinogenicity of formaldehyde is related to local effects.

RAC's response

RAC fully supports the argumentation of the DS.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	9

Comment received

The NL CA agrees with the classification for Muta 2 (H341) because treatment with RP 1:1 and RP 3:2 gave positive mutagenicity results in vitro (Ames test, chromosome aberration test and mammalian cell gene mutation test [p. 40-41 CLH Report]). The majority of available in vivo studies (cytogenetics test and micronucleus test) for RP 1:1 and RP 3:2 are negative, with the exception of the chromosome aberration study where clastogenic activity was reported in the mouse bone marrow after i.p. injection of ≥ 50 mg/kg bw (p. 43, CLH Report). Nevertheless, the MTD was not reached in any of these studies. The combination of the limited positive in vivo study for RP 1:1, the positive in vitro studies for RP 1:1 and RP 3:2 and the formation of formaldehyde classified as Muta Cat 2 warrant classification for Muta 2 (H341).

Dossier Submitter's Response

We acknowledge the support.

RAC's response
RAC takes note of the support.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	10
Comment received				
We support the proposed classification as Muta. 2. Classification as Muta Cat. 2 is supported based on the presented substance-specific information (Page 46 chapter 4.8.5) on MBO, the similarity to responses observed with formaldehyde (tables 4.8-3 and 4.8-6) and the previous classification of formaldehyde as Muta Cat. 2.				
Dossier Submitter's Response				
We acknowledge the support.				
RAC's response				
RAC takes note of the support.				

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		Individual	11
Comment received				
IV. Mutagenicity In accordance with EU CLP (Regulation (EC) No. 1272/2008) classification of MBO is not required for genotoxicity based on the absence of genotoxicity in vivo. The mutagenic potential of MBO has been evaluated using a number of in vitro assays. Two out of three Ames tests showed negativeor ambiguous result and only one indicated a weakly mutagenic activity of MBO; but MBO shows a dose-dependent mutagenic predominantly clastogenic activity with and without metabolic activation in one chromosome aberration assay with CHL cells and two mouse lymphoma assays with L5178Y TK+/- cells. In vivo studies, however, indicate that it is not genotoxic. MBO did not induce a significant increase in micronuclei in the in vivo mouse micronucleus assay in bone marrow at doses of 30, 100, 300 mg/kg. In accordance with the CLP guidance, the results from the in vivo assays on MBO in the form that it is placed on the market should be more heavily weighted as an indicator of the inherent genotoxic properties of MBO than the in vitro assays. Information presented in this paper provided sufficient reasons why it is not scientifically credible to rely on data generated from experiments involving MBO 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 MBO 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 not scientifically credible or 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 MBO, and so the proposed classification of MBO as a Mutagen is both disproportionate and not scientifically defensible. *ECHA comment: The following <u>non-confidential</u> attachments were provided with this*				

comment. Please also refer to Comments 3 and 8 [Attachments 1 – 7]

- Formaldehyde releasers: principles of chemistry and hydrolysis. A. Bitsch. Presentation, FABI Information Day 9th of December 2014, Vienna
- The situation of formaldehyde releasers and the need for a holistic approach on in-can preservatives (PT 6), Didier Leroy, FABI Information Day 9th of December 2014, Vienna
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- Short Summaries of Studies

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- Formaldehydemeasurements in the ambient air of a production facility by the use of ”Grotan OX, Schülke und Mayr“
- Study Report – Cooling lubricants – test on free formaldehyde
- Study Report – Diesel additives – test on free formaldehyde
- Study Report – MBO vs Formalin – test on identity and differences
- Study report – Diverse test items – test on free formaldehyde

Dossier Submitter’s Response

Please see our response to comment 3, which contains all considerations also with regard to this comment No 11.

Here the considerations relevant to this comment 11 are repeated.

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 4.8.3. and 4.8.4. 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 RP 3:2 also this harmonized conclusion was suggested for RP 3:2.

RAC's response
RAC agrees with the statements of the DS. It should be noted that the MS CA's classification proposals are not based on the precautionary principle and RAC does not propose precautionary classifications. Classification is based on a weight of evidence from all relevant data - either taking into account reliable data on the substance of concern itself and/or using read across from other substances.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	12
Comment received				
The increase in post-implantation loss combined with post-natal lose at the highest dose in the one-generation study is considered to be secondary to the maternal effects on the stomach by the dossier submitter. However, this is not substantiated. Therefore, it is suggested to make a comparison of the maternal and fetal/pup effects in the one-generation study for individual dams to see whether the most severely affected dams have the most fetal/pup effects. In addition, it could be considered to look for other substances which induce comparable stomach effects and look whether these substances induce comparable fetal/pup effects in a generation study.				
Dossier Submitter's Response				
A detailed analysis of this aspect was already carried out and is available in the Annex to the CLH Dossier Annex IIIA/MBOA6.8.2_1 and 6.8.2_2: On the individual animal data level this correlation of local forestomach effects with pub losses is not unequivocally confirmed.However it is concluded that the lack of concomitant findings in the fertility study and the developmental study is considered the strongest support to conclude that the increased post implantation loss at high dose does not represent a direct substance related effect.This is also explained in the CLH Dossier in chapter 4.10.1.2., last paragraph.				
RAC's response				
The proposal to consider the individual data on dams and fetus/pups was followed (see the documentation of study results in the opinion document) and a detailed analysis does not support the forestomach lesions as possible cause of the implantation losses and postnatal deaths. Post-implantation losses were also seen in the developmental study on rabbits. However, the data are not conclusive due to the high mortality at the high dose.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	13
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, please refer to formaldehyde classification as you did for the other endpoints. 4.2. 4 Acute toxicity – for the RP1:1 and RP3:2 (p.26): For acute oral toxicity point, please correct the classification based on experimental study:				

Category 3 H311.
For acute inhalation toxicity, we consider that the read across from formaldehyde is justified for this end point. However, it is unlikely that the emission rate of formaldehyde is constant over time. Therefore, MSCA-FR proposes the classification H332 for the reaction product.

Dossier Submitter's Response

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.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 be 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.

RAC's response

To the comment on acute oral toxicity, RAC agrees with the arguments put forward by France, but considers Category 4 more appropriate.

The proposal to classify for acute inhalation toxicity based on the read across to formaldehyde has been adopted by RAC, as explained in the opinion document.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	14

Comment received

The NL CA agrees with the classification for Skin Corr. 1 (H314) based on corrosive properties of the hydrolysis product formaldehyde and the irreversible skin damage observed for RP 1:1 and RP 3:2 (pg. 28-29 CLH Report). In table 1.2-1 on p. 6, Skin Corr.1B (H314) is written as the current proposal for consideration by RAC and proposed harmonized classification yet on p. 29 (Section 4.4.1.6 and 4.4.1.7), Skin Corrosive Category 1 (H314) is proposed.

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 4.2.1.2 (p. 24-25 in CLH Report) and comparison criteria provided on p. 26 (CLH report), Acute Tox. 4 (H302), Acute Tox. 4 (H312) and Acute Tox. 4 (H332) are warranted.

The Netherlands agrees that no classification for STOT SE 3 (H335) is required given that no other specific target toxicities are reported in addition to 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'. In addition, the additional labelling with EUH071 (Corrosive to the respiratory tract) already provides a warning regarding the effect 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'. The oral rat LD50 is 630 mg/kg bw with no effects found with 200 mg/kg bw (~10% solution; p.25 in CLH Report). It is stated on page 25 that no local effects were observed in the acute oral study. The 90-day oral rat LOAEC (1.2%) was 60 mg/kg bw with a NOAEC of 20 mg/kg bw (0.4%; p. 37-38 CLH Report). At 60 mg/kg bw, local effects in the stomach warranting classification were observed. In addition, rats treated with RP 3:2 in the OECD 415 study had local stomach effects (forestomach ulcerations) at 45 mg/kg bw (treatment over a 70-day preparation period, during pairing, gestation and lactation). The systemic NOAEL was 15 mg/kg bw for parents and F1. Given that local stomach effects were reported in the 90-study at 60 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

Skin Corr Cat 1: 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 categories1B/1C is foreseen). Annex VII of the CLP Regulation suggests to translate category C, R34 to Skin Corr. Cat 1B. Furthermore the hydrolysis product formaldehyde is classified in Category 1B.

Eye damage Cat1: 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: Please see our response to comment 13 above.

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 2: According to CLP Regulation, Annex I, Article 3.9.1.1. we do not suggest to classify for STOT RE 2. 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
With regards to acute toxicity, STOT SE and STOT RE the MS's suggestions were considered in the opinion document. Classification for Skin Corrosion (Cat 1 B) was adopted by RAC with a slightly different reasoning as proposed by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	15
Comment received				
We propose Classification as Skin Corr. 1 without sub-classification.The proposal presented on page 6 table 1.2-1 for sub-classification into Skin Corr. category 1B for Skin and Eye Irritation is apparently not entirely consistent with the conclusions presented in chapters 4.4.1.7 and 4.4.2.7 on pages 29 and 31, resp.. There, the no sub-classification was proposed. Considering the evidence presented, differentiation between sub-categories A/B/C would not be possible (see also chapter 4.4.1.6).				
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 categories1B/1C is foreseen). Annex VII of the CLP Regulation suggests to translate category C, R34 to Skin Corr. Cat 1B. Furthermore the hydrolysis product formaldehyde is classified in Category 1B.				
RAC's response				
Please note that the CLP Regulation currently requires subcategorisation for this hazard class. The DS argumentation is noted, but more weight has been given to the available guideline-compliant study.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	16
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 – the RAC decision on a separate classification for eye damage may be followed for future CLH reports.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2015	Netherlands		MemberState	17
Comment received				

The NL CA agrees with the classification for Skin Sens. 1A (H317) based on the GPMT for RP 3:2 with an intradermal induction of 0.5% and 60% of positive animals after challenge with a 1% solutions. According to Annex I: 3.4.2.2.3.2 for the GPMT sub-category 1A applies for ≥ 60% responding at > 0.1% to ≤ 1% induction dose.
Dossier Submitter's Response
We acknowledge the support.
RAC's response
RAC's conclusion on classification has taken into account the views of the DS, NL and DE.

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Germany		MemberState	18
Comment received				
We support the proposed classification of MBO as Skin Sens. 1A; H317. The reasons for this approval were positive results of studies using MBO as testing material and the already existing classification of hydrolysis product formaldehyde as Skin Sens. 1; H317.				
Dossier Submitter's Response				
We acknowledge the support.				
RAC's response				
See comment 17.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	19
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, please refer to formaldehyde classification as you did for the other endpoints.				
Dossier Submitter's Response				
Please see our response to comment No. 14.				
RAC's response				
It seems correct that STOT SE is not generally covered by classification for corrosivity. However, regarding respiratory tract irritation (STOT SE 3) the CLP guidance considers the potential for respiratory tract irritation as covered by the classification for corrosivity. No evidence was provided on a need for classification for STOT SE 1 or 2.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	20
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, please refer to formaldehyde classification as you did for the other endpoints.				
Dossier Submitter's Response				
Please see our response to comment No. 14.				
RAC's response				

A conclusion on classification has been included in the opinion document.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	21
Comment received				
As part of a classification dossier, we have no comments regarding environmental hazard. Nevertheless, a new algae study might be requested in an evaluation dossier				
Dossier Submitter's Response				
Thank you for your comment. If the term "evaluation dossier" refers to the draft competent authority report (CAR) for biocides we consider a new study not necessary for risk characterisation according to Regulation EU (No) 528/2012 based on the rapid hydrolyses of RP 3:2. The environmental risk characterisation for biocides was performed only with the the hydrolysis products.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2015	Finland		MemberState	22
Comment received				
Basically we support the proposed classification Aquatic Chronic 3, H412: Harmful to aquatic life with long lasting effects for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2), but we consider that further information is needed to verify the conclusion on hydrolysis. The conclusion made in the CLH Report is that the hydrolysis half-life DT50 is expected to be less than 1 hour at all pH values and that the Reaction product is to be completely hydrolysed to formaldehyde and 2-hydroxypropylamine under environmental relevant conditions. In our opinion more information is needed to confirm that conclusion: What is the pH in the test presented in Table 5.1.1-2? What are the 'concentrations expected in the environment'? What is the reasoning for assuming that 'as the equilibrium was reached within few hours in the performed test investigating a 1 % w/w solution, the hydrolysis half-life DT50 is expected to be less than one hour at all pH values under environmentally relevant conditions'. The further part of the hydrolysis test is performed at pH values 4, 7 and 9 with 1 % w/w solution. The main hydrolysis products for the 1% w/w solution are based on the first part of the test trianzine and 5-methyloxazolidine, and not formaldehyde and 1-aminopropanol (2-hydroxypropylamine) (Figure 5.1.1-2). Please, explain why the 1% w/w solution was chosen? According to the guidance IR R.7b the extrapolation of laboratory results determined at high concentrations to low environmentally realistic concentrations is permitted when hydrolysis reactions follow apparent first order reaction rates and half-lives are independent of the concentration. In this case the study results show that the equilibrium of hydrolysis is strongly dependent on the concentrations in water. Finally, since there is no adequate long term data for all three trophic levels surrogate method should be performed to assess the classification for long term hazard. The application would, however, not change the classification for Reaction product in this case.				

Dossier Submitter's Response
Table 5.1.1-2 aimed to identify the determination of the concentration-dependent composition by ^{13}C-NMR and used different proportions of Contram™ MBO and D_2O (no buffer). Contram™ MBO has a pH of around 9.0-10.0. No pH measurements have been performed prior to ^{13}C-NMR analyses. Please note that hydrolyses was studied at different concentrations including very low concentrations of 0.0025%. Concerning PEC values we calculated exposure scenarios for PT13 according to the Fraunhofer approach. However since the guidance for the exposure assessment was a draft at the time of the calculation we expect a revision of the during the commenting period of the draft CAR. The study on pH dependant hydrolysis had several challenges related to the quantitiave ^{13}C NMR measurements. Therfore the 1% solution was chosen. The half-life could not be calculated according to OECD guideline 111 because of the following reasons: 1. It is not a single compound but a mixture of compounds that release formaldehyde. 2. The initial concentration of the formaldehyde releasing compounds can not be determined since the hydrolysis is very fast and already starts druing the first ^{13}C NMR measurement. Therefore the half-life of the formaldehyde release was estimated unter the following assumptions: - The initial overall concentrations C_0 (^{13}C peak areas) of the bonded formaldehyde was equated to the final concentations (^{13}C peak area) of the formaldehyde hydrate. - The overall concentration C_t of the bonded formaldehyde at the point in time t corresponds to the difference between the final concentration of formaldehyde hydrate and the concentration at the point in time t. Please note that two NOECs für algae are available that are used for long-term aquatic hazards.
RAC's response
Noted. RAC agrees that the surrogate method may be taken into account but would not lead to a different classification.

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	United Kingdom		MemberState	23
Comment received				
We agree that the reaction product rapidly hydrolyses to formaldehyde and 2–hydroxypropylamine which are both considered rapidly degradable. For the parent reaction product to be considered as rapidly degradable the degradants should not be classified for the environment. The proposal considers both degradants are not classified for the environment and that the reaction product is therefore rapidly degradable. We feel the current CLH proposal would benefit from further information to support this position. Formaldehyde has a harmonised classification (605-00-00-5) and is not classified for environmental effects on the basis of assessment in 1997. The recent CLP harmonisation proposal focused on human health and did not include review of environmental data.				

2 –hydroxypropylamine has a harmonised classification (603-082-00-1) and is not classified for environmental effects on the basis of assessment in 1997. For both substances it is unclear if newer data is available or if the classification should be revised in light of the CLP regulation. We feel the proposal should consider the existing environmental classifications of 2 –hydroxypropylamine and formaldehyde to support the rapidly degradable position.
Dossier Submitter's Response
Thank you for your comment. To support "rapidly degradable" for RP 3:2 both hydrolysis products have data indicating ready biodegradability. For further information please see the formaldehyde core dossier, Doc II-A and the Appendix 2-hydroxypropylamine (attached in IUCLID). Formaldehyde data have been assessed by Germany as Rapporteur Member State for the Biocides Review Programme in 2012 ("Formaldehyde Core Dossier"). This evaluation does not give a justification to classify formaldehyde for environmental hazards. However for formaldehyde no NOEC for algae is available, for daphnia the NOEC is 1.04 mg/L. Algae are the most sensitive species for the formaldehyde releaser RP 3:2, RP 1:1 and MBM. For 2-hydroxypropylamine no new data could be located to justify its classification for environmental hazards. The findings from the OECD 2011 evaluation and the REACH CSR were carefully checked.
RAC's response
Noted, RAC has considered the argumentation by UK and the option to classify as aquatic chronic 2, H411.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2015	France		MemberState	24
Comment received				
1.1. Purity: P.5. FR agrees that it is difficult to define a minimum purity for this UVCB substance. Nevertheless, a range should be set for contents of each compound of the mixture reported in section B.1.2 of this CLH report				
Dossier Submitter's Response				
The active substance, which is an UVCB substance, is mainly defined by the starting materials and the reaction process. During product control the reaction mixture is specified by its formaldehyde content (42-49%.) and selected physical chemical properties (e.g., density, refractive index, etc.). These analytical methods are commonly available. In addition a more sophisticated method, namely ^{1}H and ^{13}C NMR, can be used in order to identify and quantify main constituents of the mixture. The applicant submitted a study presenting the results of a 4-batch analysis reporting concentrations for RP 3:2 (MBO), RP 1:1 (HPT) and water. All three substances together represent up to app. 60 % of the whole mixture. The applicant claimed confidentiality for this data, because it may reveal details of the manufacturing process. Therefore we did not report these data in section B.1 of the CLH-report. For more details please see "Doc III A.2 confidential" in section 13 of the IUCLID-dossier.				
RAC's response				
Noted				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE AND 2-HYDROXYPROPYLAMINE (RATIO 3:2); [MBO]

ATTACHMENTS RECEIVED

The following non-confidential attachments were provided by an Individual on 23.01.2015. Please refer to comments 3, 8 and 11

1. Formaldehyde releasers: principles of chemistry and hydrolysis. A. Bitsch. Presentation, FABI Information Day 9th of December 2014, Vienna (Filename: 1. A. Bitsch.pdf)
2. The situation of formaldehyde releasers and the need for a holistic approach on in-can preservatives (PT 6), Didier Leroy, FABI Information Day 9th of December 2014, Vienna (Filename: 2. D. Leroy.pdf)
3. The Use of Formaldehyde Releasing Biocides and Chemicals in the Oil and Gas Industry. H. Craddock. Presentation, 12.12.2014 (Filename: 3. H. Craddock.pdf)
4. Typical uses and benefits of formaldehyde releasers as metalworking-fluid preservatives. 4. S. Baumgartel. Presentation, 12.12.2014 (Fielname: 4. S. Baumgartel.pdf)
5. Statement from FABI members in response to the public consultation on potential candidates for substitution for MBM. 10.04.2014 (Filename: FABI - Input - Public consultation on potential candidates for substitution for MBM - April 2014.pdf)
6. Harmonised classification and labeling proposal for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)(MBO) comments for the public consultation from companies Lubrizol and Schülke (Filename: non-confidential-MBO comments for public consultation - 23 01 2015 clean.docx)
7. Short Summaries of Studies (Filename: Short Abstract Studies. docx)

The following non-confidential attachments were provided by FABI - Formaldehyde Biocides Interest Group on 23.01.2015. Please refer to comment 5

8. Legal & Regulatory Statement from FABI members in response to the 45 day public consultation on the proposed harmonised classification of Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) (MBO) (Filename: FABI - Legal and regulatory statement on the proposal for harmonised classification of MBO.pdf)
9. Statement supporting the comments provided by Schülke concerning the proposed harmonised classification for reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) (MBO) (Filename: FABI - Statement on the proposal for harmonised classification of MBO)

The following non-confidential attachments were provided by UNITI Bundesverband mittelständischer Mineralölunternehmen e.V. on 23.01.2015. Please refer to comment 4

10. 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) (Filename: FABI statement on harmonised classification proposal for MBO.pdf)
11. Statement of UNITI Bundesverband mittelständischer Mineralölunternehmen e.V. regarding the proposed harmonised classification and labelling of Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2), (MBO) (Filename: UNITI Statement regarding harmonised classification of RP 3-2 (MBO)_23 January 2015.pdf)

CONFIDENTIAL ATTACHMENTS RECEIVED

The following confidential attachments were provided by an Individual on 23.01.2015. Please refer to comments 3, 8 and 11

1. MBO comments for public consultation - 23 01 2015 draft (Filename: MBO comments for public consultation - 23 01 2015 draft_CONF.docx)
2. Concentration of formaldehyde in ambient air byaddition of ”grotamar 71” into diesel fuel tanks (Filename: MBO_EX_in-fuel_refilling_CONF.pdf)
3. Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO“ or „Grotan OX, Schülke und Mayr“ (Filename: MBO_EX_MWF_long-term_CONF.pdf)
4. Formaldehydemeasurements in the ambient air of a production facility by the use of ”Grotan OX, Schülke und Mayr“ (Filename: MBO_EX_MWF_short-term_CONF.pdf)
5. Study Report – Cooling lubricants – test on free formaldehyde (Filename: SMN 41210_V1_NMR_E.cooling lubricants_CONF.pdf)
6. Study Report – Diesel additives – test on free formaldehyde (Filename: SMN 41946_E_NMR Diesel Additives_CONF.pdf)
7. Study Report – MBO vs Formalin – test on identity and differences (Filename: SMN 43126_E.MBO vs. Formaline_CONF.pdf)
8. Study report – Diverse test items – test on free formaldehyde (Filename: SMN 43611_E _NMR_Grotan OX_CONF.pdf)

Attachments added by Dossier Submitter AT

1. Carcinogenicity of MBO, Justification for non-submission of data (Filename: Doc III A6.7 justif nonsub carcinogenicity.dox) *[Please refer to comment 3]*
2. List of endpoints – Formaldehyde core Dossier (Filename: DOC_I_LOEP_HCHO_core.pdf) *[Please refer to comment 1]*