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 with 2-hydroxypropylamine (ratio 1:1); [HPT]

EC Number: -
CAS Number: -

CLH-O-0000001412-86-89/F

Adopted
4 December 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE WITH 2-HYDROXYPROPYLAMINE (RATIO 1:1);[HPT]

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 with 2-hydroxypropylamine (ratio 1:1); [HPT]
CAS number: -
EC number: -
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	France		MemberState	1
Comment received				
MS-FR supports the proposed classification for skin corrosion 1B, H314 and skin sensitisation 1A, H317. Classification for acute toxicity of corrosive substances is not always redundant. Thus, in addition to classification for skin corrosivity, RP 1:1 should be classified as: Acute tox. 4 (oral) - H302 Acute tox. 3 (dermal) - H311 Acute tox. 4 (inhalation) - H332 MS-FR supports also the proposed classification for carcinogenicity, category 1B -H350 and classification for mutagenicity, category 2 -H34. FR supports the proposed classification for environment (Aquatic chronic 3).				
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 inconsistentclassification 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

With regards to the proposed classifications, the MS's suggestions were considered in the opinion document. Please note that the results from one of the two available studies on skin irritation/corrosion on RP 1:1 indicate that classification in subcategory 1C is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Germany	UNITI Bundesverband mittelständischer Mineralölöunternehmen e.V.	Industry or trade association	2

Comment received

We comment the proposed harmonised classification of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1)(HPT) with a brief attached UNITI Statement to support the attached statements of the Formaldehyde Biocid Interest Group (FABI) of 6 March 2015 regarding the proposed harmonised classificattion of HPT as Carc. 1B, H350 and Muta 2, H341 in analogy to formaldehyde.

ECHA note: The following non-confidential attachments were provided with the comment above [Attachments 4, 5 and 6]:

- *Statement of UNITI Bundesverband mittelständischer Mineralölunternehmen e.V. regarding the proposed harmonised classification and labelling of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1).*
- *FABI - Statement supporting the comments provided by Lubrizol and Schülke concerning the proposed harmonised classification for Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT).*
- *FABI - Legal & Regulatory Statement from FABI members in response to the 45 day public consultation on the proposed harmonised classification of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT).*
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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 formaldehyd

RAC's response

RAC agrees with the statements of the DS.
It is noted that the MSCA'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.

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Germany		Individual	3

Comment received

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

ECHA note: The following attachments were provided with the comment above

Non-confidential attachments [Attachments 1 – 3].

- *Short Abstract Studies*
- *non confidential version_HPT comments for public consultation -20150306 .final*
- *FABI - Input - Public consultation on potential candidates for substitution for MBM - April 2014*

Confidential attachments [Attachments 9-14]

- Study Report – Cooling lubricants – test on free formaldehyde (SMN 41210)
- Study report – Grotan – test on free formaldehyde (SMN 18537)
- Concentration of formaldehyde in ambient air by addition of "grotamar 71" into diesel fuel tanks (MBO_EX_in-fuel_refilling)
- Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO" or „Grotan OX, Schülke und Mayr" (MBO_EX_MWF_long-term)
- Formaldehyde measurements in the ambient air of a production facility by the use of "Grotan OX, Schülke und Mayr" (MBO_EX_MWF_short-term)
- HPT comments for public consultation -20150306 .final

Dossier Submitter's Response

The physical form of HPT (further described as reaction product, RP 1:1) was respected for the assessment: RP 1:1 is marketed as concentrated liquid and diluted to concentrations relevant for application. For liquids respiratory exposure via aerosols is in principle possible, in addition gaseous release and exposure to the multiconstituent RP 1:1 and hydrolysis products need to be taken into account. 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 1:1 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 RP 1:1, 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 1:1) 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 1:1 as well as the skin sensitization studies with higher diluted RP 1:1 document the biological reactivity of the formaldehyde releaser. The available hydrolysis data just indicate that highly concentrated RP 1:1 is relatively stable in water and with higher aqueous dilutions RP 1:1 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 1:1, 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 1:1 (see doc IIIA6.7. in the attachment). 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.
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Formaldehyde and RP 1:1 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 1:1 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 1:1 were neither available nor required.

It is not appropriate to consider the final in use concentration of RP 1:1 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 1:1 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 1:1 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 1:1. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for RP 1:1 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 1:1.

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 1:1 also this harmonized conclusion was suggested for RP 1:1.

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. See also comment 2.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Germany		Individual	4

Comment received

The current classification proposal is not based on the concept that HPT is inherently a carcinogen. Instead it is based on the hypothesis that human exposure to HPT liberates sufficient formaldehyde which is the carcinogenic component. Therefore the classification proposal is completely dependent on exposure factors which govern the liberation of formaldehyde. Again, it is 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 HPT based on numerous lines of evidence presented below. Further, in view of the explanation of the hydrolytic stability of HPT in the form that it is placed on the market and the very slow rate of formaldehyde-release (as a proportion of total dosed HPT) during its use as intended (i.e. in end use diluted metalworking fluid) there is demonstrably no credible scientific justification for classifying HPT as a suspected carcinogen, either in terms of direct evidence or on a weight-of-evidence approach.
1) HPT 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 indicate that HPT is not genotoxic by oral administration and the ambiguous results for intraperitoneal administration are from a dosing route that is not appropriate for the human exposure situation.
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.

However, CLP states that alternative approaches for the substance such as QSAR and Read Across predictions should be used when a substance has not been tested for carcinogenicity. The OECD Toolbox version 3.2 was used to profile HPT 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 HPT was confirmed to be not classifiable as a carcinogen.

On this basis HPT itself cannot be considered to be inherently carcinogenic by 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 HPT would occur to release sufficient formaldehyde to cause tumours. On this basis HPT itself cannot be considered to be inherently carcinogenic in accordance with the classification guidance.
4) The proposed classification of HPT 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 following chronic, repeated exposure to HPT. 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 part 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 there are no long term toxicity issues arising from formaldehyde exposure in the absence of irritation. 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.). This limits any possibility of tumour development to the naso-pharyngeal epithelium or the skin, since these are the only body surfaces that might come into contact with HPT as it can reasonably be expected to be used.

The current proposal to classify HPT 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 HPT/water solutions at very low dilutions. The measurements of "free" formaldehyde at various dilutions of HPT (see Table 1) and the occupational exposure data presented in this paper demonstrate that this hypothesis is flawed and is therefore 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). 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 scientifically credible argument that it occurs, must be a necessary pre-requisite for classifying HPT 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) also confirmed 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 HPT as a carcinogen based on release of total ('bound') formaldehyde following possible 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 HPT 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 that concentrated HPT shows only very slow hydrolysis (Hydrolysis study within dossier). Furthermore, as concentrated HPT is demonstrably corrosive to dermal skin it is reasonable to conclude that occupational exposure of the nasopharyngeal epithelium to neat HPT would result in the destruction of the epithelial cells rather than a cytotoxic effect or induction of cell proliferation which is acknowledged as a necessary precursor for tumour formation. Similarly, although there are no direct measurements of airborne mist are available for emulsions containing MBO or HPT workplace measurements of airborne formaldehyde strongly suggest that inhalation exposure to low concentrations of HPT (for example through aerosolisation of an end-use metalworking fluid containing HPT at the typical effective dose of 1500 ppm) would be well below the calculated DNEL (0.43 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 HPT in the workplace.
HPT is non-volatile (calculated vapour pressure; 4.69 10-9 hPa at 25°C calculated for the main constituent HPT by using EPI suite (Doc III A3 of the dossier) and therefore there is 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 these physical properties. Additionally aerosolisation is not a credible route of exposure to neat HPT during handling by workers when formulating a mixture or concentrate. There is however the possibility of exposure to HPT for metal workers due to aerosolisation of an end-use fluid during high energy operations such as grinding, cutting or milling. Oil mist measurements previously taken in a workshop where the metalworking emulsions contained a different formaldehyde-releaser (methylene bismorpholine, MBM) indicate that the oil mist level is very low (185 µg/m3) confirming that this unlikely to occur at sufficient level.

3. It is an unrealistic assumption that workers' nasopharyngeal epithelium will be exposed to supra-irritating levels of formaldehyde released from HPT 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 HPT. 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 HPT as a carcinogen.

Non-confidential attachments [Attachments 1 – 3].
- *Short Abstract Studies*

- *non confidential version_HPT comments for public consultation -20150306 .final*
- *FABI - Input - Public consultation on potential candidates for substitution for MBM - April 2014*

Confidential attachments [Attachments 9-14]

- Study Report – Cooling lubricants – test on free formaldehyde (SMN 41210)
- Study report – Grotan – test on free formaldehyde (SMN 18537)
- Concentration of formaldehyde in ambient air by addition of ”grotamar 71” into diesel fuel tanks (MBO_EX_in-fuel_refilling)
- Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO“ or „Grotan OX, Schülke und Mayr“ (MBO_EX_MWF_long-term)
- Formaldehyde measurements in the ambient air of a production facility by the use of ”Grotan OX, Schülke und Mayr“ (MBO_EX_MWF_short-term)
- HPT comments for public consultation -20150306 .final

Dossier Submitter’s Response

Please see our response to comment 3, which contains all considerations also with regard to this comment No 4.

Here the considerations relevant to this comment 4 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 HPT (further described as reaction product, RP 1:1) was respected for the assessment: RP 1:1 is marketed as concentrated liquid and diluted to concentrations relevant for application. For liquids respiratory exposure via aerosols is in principle possible, in addition gaseous release and exposure to the multiconstituent RP 1:1 and hydrolysis products need to be taken into account. , 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 1:1) 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

1:1 as well as the skin sensitization studies with diluted RP 1:1 document the biological reactivity of the formaldehyde releaser. The available hydrolysis data just indicate that highly concentrated RP 1:1 is relatively stable in water and with higher aqueous dilutions RP 1:1 hydrolyses to formaldehyde and 2-hydroxyl-propylamin quickly (DT50 below 1 hour). 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 1:1 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 1:1. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for RP 1:1 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 1:1.

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 1:1 also this harmonized conclusion was suggested for RP 1:1.

Formaldehyde and RP 1:1 are considered as 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 1:1 is relatively stable in water and with higher aqueous dilutions RP 1:1 hydrolyses to formaldehyde and 2-hydroxyl-propylamin quickly (DT50 below 1 hour).. 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 1:1 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 of RP 1:1. For Formaldehyde positive local in vivo genotoxicity data are available (gastrointestinal tract, respiratory tract), for RP 1:1 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 1:1. However for formaldehyde respiratory exposure was observed as the critical route for local tumour development. Respiratory studies with RP 1:1 were neither available nor required. We acknowledge the RAC conclusion that the carcinogenicity of formaldehyde is related to local effects.

RAC's response

Again, RAC fully supports the argumentation of the DS.

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	5

Comment received

The NL CA agrees with the classification for Carc. 1B (H350) for the reaction product (RP) of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1) 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 reaction mixture of RP (1:1) contains about 28% releasable formaldehyde in aqueous solution (p. 24, 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 the hydrolysis study shows that from RP 1:1, formaldehyde is formed. Therefore it is reasonable to assume that RP 1:1 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 1:1 is a liquid.

Dossier Submitter's Response

We acknowledge the support.

RAC's response

The view of NL CA has been considered.

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Belgium	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. HPT, Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1), 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 HPT could be by analogy applicable for all formaldehyde releasers.

ECHA note: The following 2 non-confidential attachments were provided with the comment above [Attachments 7 and 8]:

- FABI - Statement supporting the comments provided by Lubrizol and Schülke concerning the proposed harmonised classification for Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT)
- FABI - Legal & Regulatory Statement from FABI members in response to the 45 day public consultation1 on the proposed harmonised classification of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT)

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 HPT (further described as reaction product, RP 1:1) 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 RP 1:1 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 RP 1:1 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 RP 1:1. 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 RP 1:1 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 RP 1:1 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 RP 1:1 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.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Germany		Individual	7

Comment received

The mutagenic potential of HPT has been evaluated using a number of assays. In vitro results are indicating weak mutagenic activity although this is considered to be due to released formaldehyde in the aqueous test system.
With respect to in vivo assays, two chromosome aberration tests (oral or intraperitoneal dosing) and one mouse micronucleus assay (intraperitoneal dosing) are available but show equivocal effects. However HPT does not indicate genotoxicity after oral administration and the equivocal results for intraperitoneal administration should not be considered due to an inappropriate route of administration for human exposure.

Significantly, classification as a Mutagen according to CLP 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 HPT as a mutagen, namely the hydrolytic release of sufficient 'bound' formaldehyde leading to a level of `free` formaldehyde distant to the site of contact that is sufficient to adversely affect germ cells is not proven and means that the proposed classification is neither scientifically credible nor defensible. This is because 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 HPT, and so the proposed classification of HPT as a Mutagen is both disproportionate and not scientifically defensible.

Non-confidential attachments [Attachments 1 – 3].

- *Short Abstract Studies*
- *non confidential version_HPT comments for public consultation -20150306 .final*
- *FABI - Input - Public consultation on potential candidates for substitution for MBM - April 2014*

Confidential attachments [Attachments 9-14]

- Study Report – Cooling lubricants – test on free formaldehyde (SMN 41210)
- Study report – Grotan – test on free formaldehyde (SMN 18537)
- Concentration of formaldehyde in ambient air by addition of ”grotamar 71” into diesel fuel tanks (MBO_EX_in-fuel_refilling)
- Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO“ or „Grotan OX, Schülke und Mayr“ (MBO_EX_MWF_long-term)
- Formaldehyde measurements in the ambient air of a production facility by the use of ”Grotan OX, Schülke und Mayr“ (MBO_EX_MWF_short-term)
- HPT comments for public consultation -20150306 .final

Dossier Submitter’s Response

Please see our response to comment 3, which contains all considerations also with regard to this comment No 7.

Here the considerations relevant to this comment 7 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 1:1 also this harmonized conclusion was suggested for RP 1:1.

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 to substances with sufficient systemic availability. In addition, information is provided on whether it is possible that genotoxic effects may play a role in carcinogenesis. Therefore the guidance also regulates the *in vivo* testing as well as possible classification of substances that can only act locally in somatic cells at site of contact due to their poor systemic availability.

RP 1:1 is poorly systemically available due to its rapid hydrolysis. Accordingly, the available i*n vivo* results are of low relevance because they examine the possible induction of mutagenic effects at a distance from the site of exposure. Therefore the results do not allow the conclusion that the substance is not genotoxic in the whole animal. There is no test with RP 1:1 which assessed whether genotoxic effects will be induced in cells at the site of first contact. But for the evaluation of toxicological properties of RP 1:1 it is taken into account that its hydrolysis product formaldehyde is already classified as a Category 2 mutagen due to the induction of local genotoxic effects.

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	8
Comment received				
The NL CA agrees with the classification for Muta 2 (H341) because treatment with RP 1:1 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 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. 45-46, 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 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.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	9
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 for MBO (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 the fetus/pups was followed (see the documentation of study results in the opinion document) and a detailed analysis did not confirm the forestomach lesions as a 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
06.03.2015	France		MemberState	10
Comment received				
Acute toxicity, page 29 Classification for acute toxicity of corrosive substances is not always redundant. Thus, in addition to classification for skin corrosivity, RP 1:1 should be classified as: Acute tox. 4 (oral) - H302 Acute tox. 3 (dermal) - H311 Acute tox. 4 (inhalation) - H332 Other comments, page 21: A summary table with the name of all the mixtures used in the toxicity studies together with the batch number and the percentage of releasable formaldehyde would be helpful.				
Dossier Submitter's Response				
Please see our response to comment 1.				
RAC's response				
With regards to the proposed classifications for acute toxicity, the MS's suggestions were considered in the opinion document. Please note that for the dermal toxicity, more weight is given on the dermal acute toxicity studies on RP 1:1 instead of read across to formaldehyde.				

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Germany		MemberState	11
Comment received				
Page 29, chapter 4.2.4 concerning harmonised classification of formaldehyde: Acute inhalation toxicity: Category 3* should read: Toxic if inhaled (instead of Fatal if inhaled). Page 29, chapter 4.2.4 concerning RP1:1 and RP 3:2: Please consider classification and labelling for acute toxicity in addition to corrosivity. LD50 for acute oral toxicity was between 630 and 960 mg/kg bw (dermal 790 mg/kg bw) for the 10 % aqueous solution (100 % mortality at 2000 mg/kg bw). Regarding inhalation, according to CLP guidance, corrosive substances for which data are available indicating that the mode of toxic action was corrosivity, classification for acute toxicity and corrosivity is required. In addition to classification for acute inhalation toxicity, the substance or mixture must also be labelled as EUH071 where data are available which indicate that the mode of toxic action was corrosivity (please refer to „Guidance on the Application of CLP Criteria, Version 4.0, Nov 2013, pp 280, 282). Classification for corrosivity of a substance has to be performed in addition to classification for acute toxicity (p. 267). *ECHA note: The following <u>confidential</u> attachment was provided with the comment above. The attachment concerns comments on the confidential annex concering substance ID [Attachment 15]* - Comment from German MSCA – CLH Dossier of Reaction product of paraformaldehyde and 2-hydroxypropylamin (ratio 1:1).				
Dossier Submitter's Response				
Please see our response to comment 1.				

RAC's response
With regards to the proposed classifications on acute toxicity, the MS's suggestions were considered in the opinion document. Please note that for the dermal toxicity, the above mentioned dermal LD50 refers to RP 3:2 only. The LD50 for RP 1:1 was above 2000 mg/kg bw. More weight is given on the dermal acute toxicity studies on RP 1:1 instead of read across to RP 3:2 and formaldehyde.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	Germany		MemberState	12
Comment received				
From the data presented in Part B - Scientific evaluation of the data – classification for skin corrosion category 1 (H314) is proposed. However, in Part A of the CLH dossier 1B is listed. Please check for inconsistency. According to description in Part B, sub-categorisation is not justified. *ECHA note: The following confidential attachment was provided with the comment above. The attachment concerns comments on the confidential annex concering substance ID [Attachment 15]* Comment from German MSCA – CLH Dossier of Reaction product of paraformaldehyde and 2-hydroxypropylamin (ratio 1:1).				
Dossier Submitter's Response				
Skin Corrosion Category 1B (as concluded in Part A) was intended as final proposal. 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 requires subcategorization. The rapporteurs proposed to conclude on the available studies on RP 1:1 that suggest Skin Corr. Cat. 1 C.				

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	13
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 (pg. 3 CLH Report). In table 1.2-1 on p. 8, Skin Corr.1B (H314) is written as the current proposal for consideration by RAC and proposed harmonized classification yet on p. 32 (Section 4.4.1.6 and 4.4.1.7), Skin Corrosive Category 1 (H314) is proposed. guidance chapter 3.3.2.4.				

Dossier Submitter's Response
Please see our response to comment 12.
RAC's response
See comment 12.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	14
Comment received				
In our opinion classification for serious eye damage (Cat. 1) is required but no labelling as explained in the CLP				
Dossier Submitter's Response				
We respect the text in the CLP Guidance (Section 3.3.2.4.) 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?				
RAC's response				
The view of the MS corresponds to the CLP and is taken forward to the opinion document.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	15
Comment received				
The NL CA agrees with the classification for Skin Sens. 1A (H317) based on the GPMT for RP 1:1 with an intradermal induction of 1% and 90% of positive animals after challenge with a 1% solution (Table 4.6-1, p.35). 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				
Will be taken forward.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	16
Comment received				
The NL CA 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 4.2.1.1 (p. 26-27 in CLH Report) and comparison criteria provided on p. 29 (CLH report), Acute Tox. 4 (H302) 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 960 mg/kg bw (~10% solution; p.28 in CLH Report). In the 90-day oral gavage study in rats (Table 4.7-1, p. 38-39 CLH Report), local effects in the larynx, pharynx and oesophagus and lethality were reported with a NOAEL of 30 mg/kg bw and an LOAEL of 80 mg/kg bw. Given that lethality and local effects were reported in the 90-study at 80 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

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 the proposed classifications on acute toxicity, STOT SE and STOT RE the MS's suggestions were considered in the opinion document.
Just to mentioned: The harmonised classification on formaldehyde is Acute Tox. 3.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2015	Netherlands		MemberState	17

Comment received

The NL CA 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 4.2.1.1 (p. 26-27 in CLH Report) and comparison criteria provided on p. 29 (CLH report), Acute Tox. 4 (H302) 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 960 mg/kg bw (~10% solution; p.28 in CLH Report). In the 90-day oral gavage study in rats (Table 4.7-1, p. 38-39 CLH Report), local effects in the larynx, pharynx and oesophagus and lethality were reported with a NOAEL of 30 mg/kg bw and an LOAEL of 80 mg/kg bw. Given that lethality and local effects were reported in the 90-study at 80 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
Please see our response to comment 16.
RAC's response
See comment 16

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
02.03.2015	United Kingdom		MemberState	18

Comment received

EHCA's Guidance on the Application of the CLP Criteria (Version 4.0, November 2013) states that 'results of biodegradability tests on complex or multi-constituent substances should be carefully evaluated before use for classification purposes is considered'. The test item Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1), (referred to here as RP 1:1) is a UVCB and as such classification of the substance as 'rapidly degradable' on the basis of a Ready Biodegradation study requires detailed evaluation.

As presented in the CLH report, 2 ready biodegradation studies following OECD Test Guideline 301B are available. The first study [Carl Becker Chemie (2002)] achieved 29-30% degradation, while the second study [Schülke & Mayr GmbH (2001)] achieved 62.7% degradation. As acknowledged by the CLH authors, both studies followed the same guideline and they considered the inoculum the only difference with both inoculums being valid. Consequently, the CLH authors consider the second study sufficient to consider RP

1:1 'rapidly degradable'. We do not support this position at this time as we feel the Schülke & Mayr GmbH (2001) positive result study does not clearly represent the good scientific quality required to supersede the negative result for the following reasons.

The study is quoted as GLP although we note it was run at an Indian facility in 2001 before the OECD Mutual Acceptance of Data for GLP in 2011. The study used potassium hydrogen phthalate as a reference substance although we note the OECD test guideline states 'Potassium hydrogen phthalate has been proposed but more evidence needs to be obtained with this chemical before it can be accepted as a reference compound.'. The study inoculum was river water from the Daman Ganga river in India not the OECD Guideline preference of secondary effluent from a domestic waste water treatment plant or laboratory-scale unit. The CLH report highlights that the river receives industrial waste effluent and it is not possible to rule out adaption of the inoculum to the test item. In addition to the 2 ready biodegradation studies for RP 1:1, 2 further ready biodegradation studies are available in the CLH Report for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2) which show only 56 and 30% degradation. We are unclear how or why this limited difference in ratio would substantially affect the potential of this UVCB for ready biodegradation.

Overall, without further support for the reliability and 'representativeness' of the Schülke & Mayr GmbH (2001) study, we do not feel RP 1:1 can be considered rapidly degradable for the purpose of classification.

Following this, we note the rapid hydrolysis of the test substance to known degradants formaldehyde and 2–hydroxypropylamine. Given this we feel the classification of RP 1:1 should consider this and be consistent with the classification approach for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2). This should include review of available fate and ecotoxicity data for the degradants – including data reviewed for classification under DSD in 1997 and newer more recently available data.

Dossier Submitter's Response

Thank you for your comment. Please consider additional information for formaldehyde and 2-hydroxypropylamine in "Appendix HPA (including HPA doc IIA, doc IIIA)"Appendix Formaldehyde (including formaldehyde core dossier IIA, IIIA)". Both documents show robust evidence that these two substances are readily biodegradable.

We consider the results for both RP 1:1 and RP 3:2 in line because the results of the respective studies are somehow comparable considering the variations of the same labs. Highest reported degradation values were reported by Jai Research Foundation for RP 1:1 and by Institute Fresenius for RP 3:2 (that were slightly below the threshold of 60% degradation). So the results are within the variations reported by the two labs. (Jai Research Foundation: 62.7% and 30% degradation for RP 1:1 and RP 3:2; Institute Fresenius: 29-30% and 56% for RP 1:1 and RP 3:2); for RP 3:2 also the reference substance potassium hydrogen phthalate was used by Jai Research Foundation.
Maybe it is worth also to consider the result of another FA-releasing substance of N,N'-methylenebismorpholine (CLH report was also submitted by AT). OECD 301B test results show that MBM was readily biodegradable (93% degradation). MBM also hydrolyses rapidly in water to an aldehyde (DT50 <1 day).

The proposed reference compounds in OECD 301 (1992) aniline, sodium acetate and sodium benzoate, though widely accepted and recommended, all degrade in the biodegradability tests even when no inoculum is deliberately added. This can also be not

considered as an optimal reference compound from a scientific point of view.

Concerning the comment that MAD was signed by INDIA in 2011 we agree that this is a critical issue concerning the acceptance of GLP. However since several studies were performed by this lab (also e.g. study HPT - Doc III A7.4.1.3/2 in section 5.4.3 and also studies for the CLH Report on RP 3:2) evaluation should be harmonized concerning GLP acceptance for the other studies as well.
Since the study in question was well document and validity criteria were met we rated the study with Klimisch score 2.

Concerning classification RP 1:1 is rapid degradable also because of abiotic degradation (hydrolysis), so the classification proposal would not be effected.

RAC's response

Noted, RAC will consider the argumentation by UK on the scientific quality and reliability of the study on ready biodegradation. We also will consider the the argumentation by UK and the option to classify as aquatic chronic 2, H411.

Date	Country	Organisation	Type of Organisation	Comment number
06.03.2015	France		Member State	19

Comment received

FR supports the proposed classification for environment : Aquatic chronic 3
We have minor comments below:
p.58: Hydrolysis in water: could you please add an explanation about the choice of dilution of 1% w/w used in the test showing the time-dependence of formation of formaldehyde? Could the results be different if this test is performed at different dilutions?
p.62: eCA mention that "the active substance is considered as readily biodegradable. This is further supported be the readily biodegradation of the hydrolysis products (see below)". However, no further data about the readily biodegradation of the hydrolysis products are presented in the CLH report. Due to the conflicting results of the 2 studies, these biodegradation data of the hydrolysis products could be added to support the conclusion.

Dossier Submitter's Response

Please note that hydrolysis was examined at different dilutions and pH-values as described in section 5.1.1. PH-dependency was examined with a 1% w/w solution because of analytical challenges. We expect that the overall finding concerning pH dependant hydrolysis would also be valid for other dilutions however at lower concentrations the extent and probably the rate (depending on water excess) would be different.

We agree with your proposal that more information on biodegradation of formaldehyde and 2-hydroxypropylamine would support the conclusion. This information is compiled in the attached documents "Appendix HPA (including HPA doc IIA, doc IIIA)" and "Appendix Formaldehyde (including formaldehyde core dossier IIA, IIIA)".

RAC's response

Noted.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION PRODUCTS OF PARAFORMALDEHYDE WITH 2-HYDROXYPROPYLAMINE (RATIO 1:1);[HPT]

Date	Country	Organisation	Type of Organisation	Comment number
05.03.2015	Sweden		Member State	20
Comment received				
The Swedish CA supports the German CA´s proposal that classification of Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1) as Aquatic Chronic 3 (H412): Harmful to Aquatic life with long lasting effects, is warranted. This conclusion is based on chronic studies on algae and that the substance is rapidly degradable. The SE CA agree that classification in Aquatic acute is not warranted since for all three tropic levels L(E)C50 values>1 mg/L are available.				
Dossier Submitter's Response				
Thank you for supporting the Austrian CA´s proposal.				
RAC's response				
Noted.				

NON-CONFIDENTIAL ATTACHMENTS RECEIVED

The following attachments were submitted on 06.03.2015 by an Individual on behalf of two companies Lubrizol Limited and Schülke & Mayr GmbH *[Please refer to comment 3, 4, 7]*

1. Short Abstract Studies (Filename: Short Abstract Studies)
2. non confidential version_HPT comments for public consultation -20150306 .final (Filename: non confidential version_HPT comments for public consultation -20150306 .final)
3. FABI - Input - Public consultation on potential candidates for substitution for MBM - April 2014 (Filename: FABI - Input - Public consultation on potential candidates for substitution for MBM - April 2014)

The following attachments were submitted on 06.03.2015 by UNITI Bundesverband mittelständischer Mineralölounternehmen e.V. *[Please refer to comment 2]*

4. Statement of UNITI Bundesverband mittelständischer Mineralölunternehmen e.V. regarding the proposed harmonised classification and labelling of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1). (Filename: UNITI Statement on the proposal of harmonised classification of RP 1-1 (HPT)_6 March 2015)
5. FABI - Statement supporting the comments provided by Lubrizol and Schülke concerning the proposed harmonised classification for Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT). (Filename: FABI - Statement on the proposal for harmonised classification of HPT (2))
6. FABI - Legal & Regulatory Statement from FABI members in response to the 45 day public consultation on the proposed harmonised classification of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT). (Filename: FABI - Legal statement on the proposal for harmonised classification of ...)

The following attachments were submitted on 06.03.2015 by FABI - Formaldehyde Biocides Interest Group *[Please refer to comment 6]*

7. FABI - Statement supporting the comments provided by Lubrizol and Schülke concerning the proposed harmonised classification for Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT) (Filename: FABI - Statement on the proposal for harmonised classification of HPT)
8. FABI - Legal & Regulatory Statement from FABI members in response to the 45 day public consultation1 on the proposed harmonised classification of Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1) (HPT) (Filename: FABI - Legal statement on the proposal for harmonised classification of HPT)

CONFIDENTIAL ATTACHMENTS RECEIVED

The following confidential attachments were submitted on 06.03.2015 by an Individual on on behalf of two companies Lubrizol Limited and Schülke & Mayr GmbH *[Please refer to comment 3, 4, 7]*

9. Study Report – Cooling lubricants – test on free formaldehyde (SMN 41210) (Filename: SMN 41210_V1_NMR_E.cooling lubricants_CONF)
10. Study report – Grotan – test on free formaldehyde (SMN 18537) (Filename: SMN18537-Grotan-_CONF)
11. Concentration of formaldehyde in ambient air by addition of ”grotamar 71” into diesel fuel tanks (MBO_EX_in-fuel_refilling) (Filename: MBO_EX_in-fuel_refilling_CONF)
12. Measurements of Formaldehyde in the air of a production room by use of the bactericide „Lubrizol CONTRAM MBO“ or „Grotan OX, Schülke und Mayr“ (MBO_EX_MWF_long-term) (Filename: MBO_EX_MWF_long-term_CONF)
13. Formaldehyde measurements in the ambient air of a production facility by the use of "Grotan OX, Schülke und Mayr“ (MBO_EX_MWF_short-term) (Filename: MBO_EX_MWF_short-term_CONF)
14. HPT comments for public consultation -20150306 .final (Filename: HPT comments for public consultation -20150306 .final_CONF)

The following confidential attachment was submitted by the German MSCA on 06.03.2015 *[Please refer to comment 11, 12]*:

15. Comment from German MSCA – CLH Dossier of Reaction product of paraformaldehyde and 2-hydroxypropylamin (ratio 1:1). (Filename: DE-MSCA Comments CLH-Dossier HPT_Confidential_CONF)