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

Executive Summary

MBO belongs to a category of biocidal actives known as formaldehyde-releasers (or formaldehyde-donors) (FAR). These substances control microbial activity by the release of formaldehyde when diluted to their effective concentration.

The different members of the formaldehyde-releasing biocides category exhibit different release characteristics and these are dependent on several factors including amongst others the type of chemical structure (N-formal or O-formal), the concentration of biocide, the dilution needed for hydrolysis and fluid pH.

MBO has been on the market in the EU since 1976 and is used to control bacterial growth in water-based metalworking fluids and fuel at a maximum end use fluid concentration of 1500 ppm (0.15%).

MBO as manufactured is a complex reaction mixture (UVCB-Substance) with only traces of “free” formaldehyde within the active substance itself. The composition of the mixtures is driven by the ratio of the starting materials. At molar ratio formaldehyde: 2-hydroxypropylamine 3:2, mainly 3,3'-methylenebis(5-methyloxazolidine) is formed. In aqueous solutions a dynamic equilibrium is formed whose composition depends on the concentration, pH value and temperature. Pure MBO contains 45% `releasable` formaldehyde per molecule, regardless the maximal amount of formaldehyde it could be shown in recent studies that ´free ´(unbound) residual formaldehyde is present less than 0.01% by weight. **(SMN 43611, SMN 43126_E)**

The motivation to develop formaldehyde releasers was to create depot substances that slowly deliver small portions of formaldehyde over a long period of time.
In addition, it was shown that the theoretical calculated maximum level of formaldehyde is practically not released and stays far below the critical amount of 0.1% free formaldehyde hydrate under real-world conditions of use. (**Hydrolysis study within dossier)**

MBO has a low volatility (low vapour pressure and Henry’s Law Constant) and is considered to be relatively stable in metalworking fluid concentrates and end use fluids. It’s efficacy especially in metalworking fluid has been shown in various efficacy tests and it’s stability in the use phase is proven by a long period of efficacy where no

further active ingredient is required in metalworking. (Referenced by common experience from downstream users)

Occupational measurements which were not included in the Competent Authority Report that was submitted to the Biocidal Product Committee is presented in this paper. These demonstrate that MBO is relatively stable in the form in which it is "reasonably expected to be used" (i.e. its intended use) and which would potentially result in the highest exposure of humans to the non-volatile MBO via aerosolisation in an end use metalworking fluid emulsion. This shows that hydrolysis is dependent on various factors in the environment as well as the surrounding and the equilibrium is not a simple fact with a fixed number.

The hydrolysis study used to justify the proposed harmonised classification of MBO as a carcinogen and mutagen, that *sufficient* formaldehyde would be released from MBO by contact with nasal mucosa to cause an adverse toxicological event, is only a more or less simple model or a surrogate for the behaviour in the environment or in living organisms and is oversimplified.

Critically, it also demonstrate that all 'bound' formaldehyde is <u>not</u> released instantaneously upon contact with water in the end use fluid. There is therefore insufficient exposure (bioavailability) to MBO by the inhalation route to give scientific credibility to the classification proposal based on total releasable formaldehyde.;

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

With the exception of skin irritation/corrosion hazard classification, the current harmonised classification proposal is entirely reliant on the assumption by the evaluation Competent Authority that a rapid hydrolysis of MBO in contact with moisture of skin or mucous membranes releases instantaneously a critical amount of formaldehyde, and that *sufficient* formaldehyde reaches relevant biological tissues to exert an adverse toxicological effect. The information presented here demonstrate that this is a significant oversimplification of what happens when MBO (or another formaldehyde donor) is used in the workplace (i.e. in the form that it is placed on the market or can reasonably be expected to be used). While the RAC has previously considered the

hydrolysis by-products when assessing the hazard classification of other substances, it has done so in the context of specific acute inhalation hazard associated with its intended use (e.g. metal phosphides generating phosphine gas for use as a fumigant). The release characteristics demonstrated by MBO in aqueous metalworking fluid emulsions under in-use conditions means that a similar approach is not justified in this case, especially for the proposed classification as a carcinogen which relies on chronic exposure of workers´ nasopharyngeal epithelium to *sufficient* 'released' formaldehyde (i.e. at a supra-threshold level).

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

I. Use and Hydrolytic Stability

MBO is an active substance which is sold as MBO in a pure form and as formulated in biocidal products, with intended uses in the preservation of fuels (<0.1% w/w final concentration in fuels) as well as the preservation of emulsifiable metalworking fluids (0.15% w/w final concentration in end use metalworking fluid). Aerosolisation of metalworking fluid emulsions in high energy applications (e.g. milling, grinding, cutting etc.) presents the most opportunity for exposure of workers to the non-volatile MBO. In metalworking applications, MBO is added up to a 1,500 ppm final concentration of the product in the end use fluid. It is critical to recognise that experimental data demonstrates that there is no discernible hydrolysis of MBO and therefore negligible release of ´bound´ formaldehyde in the form that MBO is manufactured and placed on the market. As manufactured it has less than 0.01% (wt) formaldehyde and the available data conclusively demonstrate that MBO as placed on the market is stable.

Although laboratory based hydrolysis test data with pure water demonstrates that MBO undergoes rapid hydrolysis at high dilution, it is misleading to extrapolate this finding for classification purposes. This is because "in use" formulations are a not entirely aqueous but instead consist of complex metalworking emulsions.
Experiments, which have not been submitted to Competent Authorities clearly show that MBO releases less than the critical amount of 0.1% free formaldehyde hydrate and therefore seams to be relative stable under used conditions. **(SMN 41946) (SMN 41210)**

Industry experience with MBO also supports this observation since normal fluid maintenance schedule requires the addition of fresh biocide only after a relatively long period of time to maintain fluid integrity. Formaldehyde is readily biodegradable in an aqueous medium (93% degradation based on CO_2 measurements within 28 days) and

can be depleted through microbial metabolic pathways. It is therefore indisputable that if MBO at the effective dose hydrolysed immediately upon formulation to release all 'bound' formaldehyde (which is what is suggested by the hydrolysis study presented in the dossier) then additional biocide would be required within a short space of time to maintain fluid integrity. Additionally, although the reason for the observation by end users that MBO is capable of providing longer-lasting antimicrobial activity in metalworking emulsions and other hydrocarbon-based solutions when used at the effective does is not fully understood, it is demonstrable that under conditions of normal use formaldehyde is released gradually into the end use fluid resulting in a very slow depletion of the biocide reserve (i.e. the ´bound´ formaldehyde) rather than there being an immediate release of all available (´bound´) formaldehyde upon contact of MBO with moisture as suggested by the hydrolysis study presented in the dossier.

Finally, the fact that the release of formaldehyde from MBO only occurs under certain in-fluid conditions that gradually develop over a period of time means that instantaneous release of total (bound) formaldehyde cannot be considered an *intrinsic property* of MBO (Onyekwelu et al. 1981).This observation and logic is equally applicable to other substances belonging to the formaldehyde releaser category.

This clearly demonstrates that it is an oversimplification to suggest that all dosed MBO instantaneously releases all 'bound' formaldehyde upon contact with water in the metalworking fluid aqueous emulsion, as suggested by the hydrolysis study cited in the harmonisation proposal.

It follows therefore that any hazard classification based on an assumed immediate/instantaneous release of a *sufficient* amount of 'bound' or 'releasable' formaldehyde leading to the formulation of sufficient ´free´ formaldehyde at the nasal epithelium cell surface *to cause adverse effects* also cannot be considered an intrinsic property of MBO. With reference to section sections 3.5.2.3.2 and 3.6.2.2.1 of the CLP Regulation *(CLP uses the term "hazard classification" to indicate that only the intrinsic hazardous properties of substances or mixtures are considered)* classification of MBO as hazardous on this basis in the absence of any other conclusive evidence contradicts the concept of hazard classification as defined by CLP. The classification of MBO must instead be based solely on the level of residual formaldehyde present in the substance *as placed on the market* (which is <<0.1%).

Table 1

Determination of "free" formaldehyde in MBO as manufactured and at commercially-relevant dilutions.		
Concentration of MBO	max. releasable formaldehyde, calculated	"free" formaldehyde, detected

100% MBO as manufactured (UVCB-substances)	47%	<0.01% (<100ppm)*
1% MBO	0.47%	0.098%**
0.25% MBO	0.1175%	0.0425%**
0.025% MBO	0.01175%	0.0055%**
0.0025% MBO	0.001175%	0.00074%**
* SMN 43126_E ** Hydrolysis Study		

II. Exposure and Availability Assessment

Ordinarily exposure considerations have no part to play in the classification of a substance ("unless a chemical can be considered as not being biologically available") because CLP define hazard classification to be based on the *inherent properties* of the substance in question. However, the proposal by the evaluating Competent Authority to classify MBO for carcinogenicity and mutagenicity introduces an exposure element because there is an absolute requirement for complete and immediate hydrolysis of MBO in contact with biological tissues generating *sufficient* released formaldehyde to have a site-specific localised effect. As this is the sole basis for the proposed classification as Carcinogen Category 1B and Mutagen Category 2 it is equally relevant for exposure considerations to be explored further.

Exposure Studies

Lubrizol and Schülke have generated various workplace exposure data that demonstrate typical occupational exposure of workers in respect to the critical hydrolysis product formaldehyde. The full study reports have been provided to this consultation separately and brief details of the exposure studies are given below:

Reference values Formaldehyde	
Occupational exposure SCOEL (2008)	0.2ppm (8h)
Occupational exposure SCOEL (2008)	0.4ppm (15min)
OEL air level (WHO)	0.4ppm
AEC-Formaldehyde core dossier	0.12 mg/m^3 = 0.1ppm

-when refilled (concentrate) (MBO_EX_in-fuel_refilling)

Within this experiment the formaldehyde exposition in ambient air of employees was simulated by means of adding MBO to a vehicle tank that was filled with diesel and locating it in a factory room. No significant amount of formaldehyde can be found in the air and thus no significant amount of formaldehyde can have contact with human tissue.

-in use (MWF) long-term and short term (**MBO_EX_MWF_long-term; MBO_EX_MWF_short-term)**

Measurement of formaldehyde exposure during use of a metalworking fluid containing MBO under real use conditions.

Both values, short-term as well as long term are far below the OEL air level of 0.4 ppm and below the AEC derived for the Formaldehyde core dossier (AEC 0.12 mg/m³).

Additionally, it is well known that the human body naturally produces formaldehyde (O'Sullivan et al. 2004; Cloos et al. 2008; Hou and Yu 2010) and that formaldehyde detoxification by cellular enzymes (Friedenson 2011; MacAllister et al. 2011) results in a steady state balance between formaldehyde-generating and formaldehyde-disposing processes leading to normal blood formaldehyde concentrations of around 0.1 mM (Heck and Casanova 2004). One of the primary means of formaldehyde disposition is from exhalation meaning that there is clearly a level below which no adverse effects of formaldehyde can be detected. For instance, measurements of exhaled formaldehyde in a subset of the human population show significant levels of exhaled formaldehyde ranging from 1–10 µg/m3 (Kuhsch et al. 2008) exclusive of contribution from MBO. These data are supported by further studies conducted by Moser et al. (2005).

In further support of a limit for significant toxicological events, sub-chronic studies conducted in rhesus monkeys have shown that blood formaldehyde concentration was not measurably altered by exposure to airborne formaldehyde at 6 ppm (7.37 µg/m^3) for 6 hr/day, 5 days/week for 4 weeks (Casanova-Schmitz et al. 1984). The apparent steady state of formaldehyde, even in the face of significant exposures, means that normal physiological processes can tolerate levels in excess of those considered safe by the authorities, and maximum levels of formaldehyde that can be generated by exposure to MBO under reasonably expected conditions of use. This is not surprising since the formaldehyde metabolic pathway describes several enzymatic processes that serve to ameliorate physiological formaldehyde concentrations (Tenga et al. 2001).
It is therefore demonstrably disproportionate to consider classifying MBO as a carcinogen as a means of worker protection based on a concept of total releasable formaldehyde

In addition to the numerous studies that support no delivery of inhaled formaldehyde to distant site, and combined with the fact that formaldehyde naturally occurs throughout the body and throughout the natural environment, it is also important to note that the nasal mucus effectively provides a barrier to ameliorate the adverse effect of potential formaldehyde exposure rather than just providing a source of moisture to release formaldehyde locally at the nasopharyngeal epithelium cell surface following inhalation exposure to MBO (Priha et al. 1996).

This observation adds to the weight-of-evidence that insufficient formaldehyde released following inhalation exposure to MBO is available to cause toxicologically-relevant adverse effects in the nasopharyngeal epithelium.

III. Carcinogenicity

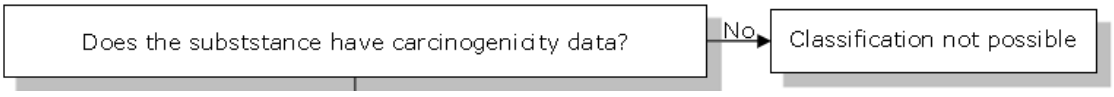
The current classification proposal is not based on the concept that MBO is inherently a carcinogen but that human exposure liberates formaldehyde which is the carcinogenic component. Therefore the classification proposal is dependent on exposure factors which govern the liberation of formaldehyde. It 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.

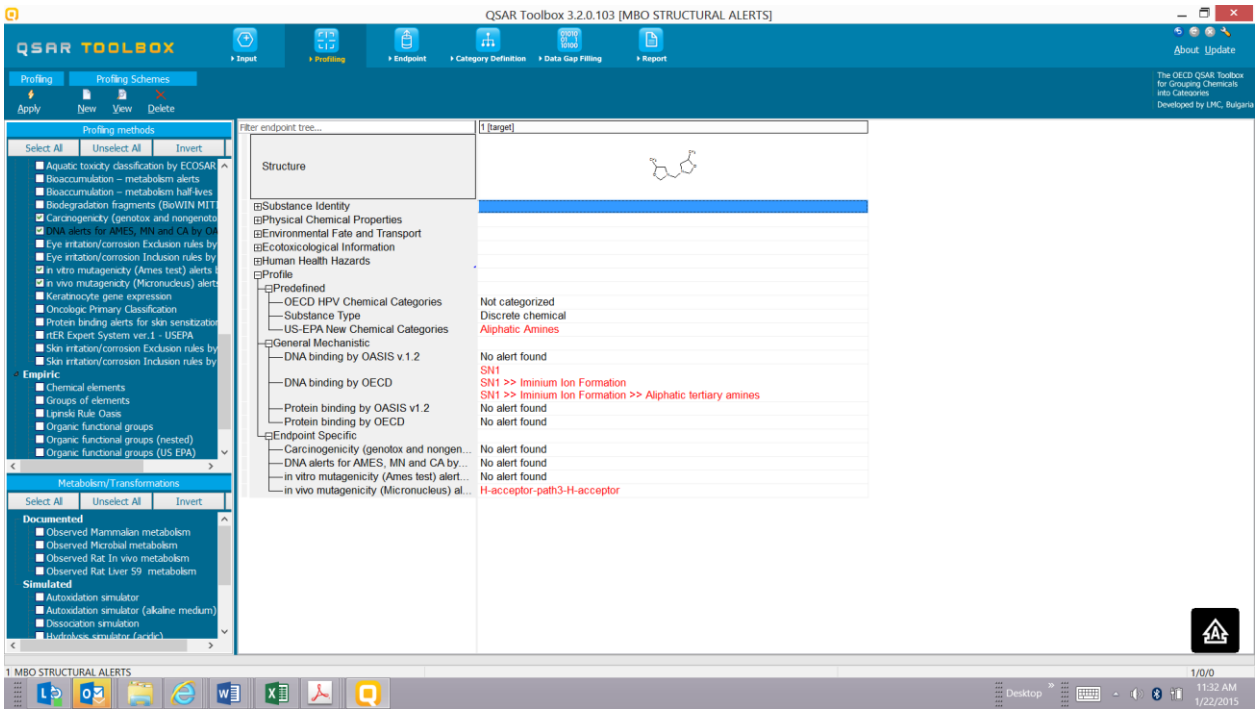
1) MBO as manufactured and in the form that is placed on the market contains less than 0.1% 'free' or 'unbound' formaldehyde as an impurity.
2) CLP states that "carcinogenic potential can be inferred from in vivo and in vitro …mutagenicity studies". In vivo studies demonstrate that MBO is not genotoxic 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.

3.6.2.6. Decision logic for classification of substances

The decision logic which follows is taken from the GHS Guidance. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.



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.

IV. <u>Mutagenicity</u>

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.

V. <u>Administrative Argument</u>

The intent of CLP is to provide a high level of protection of human health. This is achieved by classifying substances (and mixtures) for hazard classes and categories based on the *intrinsic hazard* of the substance *as placed on the market* or in the *form that it can reasonably be expected to be used*. Additionally, CLP states that classification should be achieved using a weight of evidence approach involving expert judgment, especially in those circumstances where criteria cannot be applied directly such as in the absence of relevant test data. CLP also recognises that for reasons of proportionality and workability there is a level below which identified impurities should not be considered in determining the hazard classification of substances and mixtures (i.e. 0.1 wt% for carcinogens). In other words, CLP's authors recognised that to make the system workable (practical) for worker safety purposes a specific threshold should apply to all hazard categories, even for carcinogens. It is therefore proportionate and reasonable that the same consideration should be applied to MBO for the hazard classes under consideration: in other words, MBO should be classified for carcinogenicity, mutagenicity and skin sensitisation based upon the amount of residual (i.e. unreacted or unbound) formaldehyde present in the

substance *as it is placed on the market and can be reasonably be expected to be used* rather than being classified based on the inappropriate extrapolation of one data point (i.e. hydrolysis) as the basis of an unproven assumption that there would be instantaneous release of all 'bound' formaldehyde following the hydrolysis of MBO on contact with biological tissue.

VI. Impact of the classification as CMR (Informationday)

The members of the CEFIC Formaldehyde Biocides Interest Group (FABI) invited to an information day on formaldehyde and formaldehyde releasers in December 2014. This one-day workshop gave a good overview of the uses and benefits of formaldehyde and formaldehyde releasers as biocidal active substances.

Several experts from industry and downstream user associations provided insight into the benefits, efficacy and safe use of formaldehyde and its releasers in the different biocidal applications supported under the review programme. Please find some of the slides of the workshop within the public attachment section of our comment for more detailed information.

1. Formaldehyde releasers: principles of chemistry and hydrolysis
Annette Bitsch, Fraunhofer Institute for Toxicology and Experimental Medicine ITEM

2. The situation of formaldehyde releasers and the need for a holistic approach on in-can preservatives (PT 6)
Didier Leroy, Technical Director, CEPE

3. The Use of Formaldehyde Releasing Biocides and Chemicals in the Oil and Gas Industry
Henry Craddock, HC Oilfield and Chemical Consulting

4. Typical uses and benefits of formaldehyde releasers as metalworking-fluid preservatives (PT 13)

5. Safe and essential use of formaldehyde releasers in metalworking-fluid preservatives (PT 13)
Stephan Baumgärtel, Union of the European Lubricants Industry (UEIL)

Further Information on this topic in respect of candidate for substitution, which is only one consequence of the reclassification as CMR can be found in the FABI Statement from April 2014. This statement has been already submitted by FABI in response to the public consultation for the formaldehyde releaser MBM and can also be found as a public attachment.

References:

Bogdanffy, M.S., P.H. Morgan, T.B.Starr, and K.T. Morgan. (1987). Binding of formaldehyde to human and rat nasal mucus and bovine serum albumin. Toxicol. Lett. 38(1-2):145-154.

Casanova-Schmitz, M, T. B. Starr, and H. Heck. (1984). Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [14C]- and [3H] formaldehyde. Toxicol. Appl. Pharmacol. 76:26-44.

Casanova-Schmitz M, David RM, Heck Hd'A (1984) Oxidation of formaldehyde and acetaldehyde by NAD+-dependent dehydrogenases in rat nasal mucosal homogenates. Biochem. Pharmacol. 33: 1137-1142.

Cloos P. A., Christensen J., Agger K. and Helin K. (2008) Erasing the methyl mark: histone demethylases at the center of cellular differentiation and disease. Genes Dev. 22, 1115–1140.

Heinz-Peter Gelbke, Sibylle Gröters, Peter Morfeld (2014). Lowest adverse effects concentrations (LOAECs) for formaldehyde exposure. Regulatory Toxicology and Pharmacology. Volume 70, Issue 1, October 2014.

Heck H and Casanova M (2004) The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant site toxicity. Regul. Toxicol. Pharmacol. 40: 92-106.

Heck HD, Casanova-Schmitz and M, Dodd PB, Schachter EN, Witek TJ, Tosun T (1985) Formaldehyde (CH2O) concentrations in the blood of humans and Fischer-344 rats exposed to CH2O under controlled conditions. Am. Ind. Hyg. Assoc. J. 46: 1-3.

Hou H. and Yu H. (2010) Structural insights into histone lysine demethylation. Curr. Opin. Struct. Biol. 20, 739–748.

Levgeniia Kushch, Konrad Schwarz, Lukas Schwentner, Bettina Baumann, Alexander Dzien, Alex Schmid, Karl Unterkofler, Günter Gastl, Patrik Spanel, David Smith and Anton Amann (2008) Compounds enhanced in a mass spectrometric profile of smokers' exhaled breath versus non-smokers as determined in a pilot study using PTR-MS. Journal of Breath Research V2, No. 2.

Moser B et al. (2005). Mass spectrometric profile of exhaled breath – field study by PTR-MS. Respiratory Physiology and Neurobiology, 2005, 145:295–300.

NRC 2011. National Research Council, Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde; Board on Environmental

Studies and Toxicology; Division on Earth and Life Studies; National Research Council. NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES. THE NATIONAL ACADEMIES PRESS. Washington, D.C.

O'Sullivan J., Unzeta M., Healy J., O'Sullivan M. I., Davey G. and Tipton K. F. (2004) Semicarbazide-sensitive amine oxidases: enzymes with quite a lot to do. Neurotoxicology 25, 303–315.

Onyekwelu, I. U., E. O. Bennett, and J. E. Gannon. (1981) The effective life of preservatives in cutting fluids due to the accumulation of microbial metabolism by-products. Tribiology International 14(1), 7-9.

Priha E, Liesivuori J, Santa H, Laatikainen R.(1996) Reactions of hydrated formaldehyde in nasal mucus. Chemosphere. Mar;32(6):1077-82.

RAC 2012. Committee for Risk Assessment RAC Annex 1 Background document to the Opinion proposing harmonised classification and labelling at EU level of Formaldehyde EC number: 200-001-8 CAS number: 50-00-0 CLH-O-0000003155-80-01/A. Adopted 28 November 2012.

Tenga S, K. Bearda, J. Pourahmada, M. Moridania, E. Easson, R. Poonb, P. O'Brien, (2001) The formaldehyde metabolic detoxification enzyme systems and molecular cytotoxic mechanism in isolated rat hepatocytes. Chemico-Biological Interactions. Volumes 130–132, 30 January 2001, Pages 285–296.