

Harmonised classification and labeling proposal for Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1) (HPT) comments for the public consultation from companies Lubrizol and Schülke

This comment relates to HPT but it is also appropriate to reference the Reaction product of paraformaldehyde and 2-hydroxypropylamine in the ratio 3:2 (known as MBO). This is because MBO and HPT are made from the same raw materials using different ratios. One difference between these two substances is the content of 'releasable' (bound) formaldehyde; MBO contains 45 % 'releasable' formaldehyde whereas HPT contains only 28% 'releasable' formaldehyde. Therefore, the exposure studies performed with MBO and cited in these comments represent a "worst case" scenario due to the higher content of 'releasable' formaldehyde. MBO has been the subject of a recent harmonised classification proposal and a separate statement concerning this proposal has already been sent to ECHA during the public consultation period. Further information on the formaldehyde release characteristics of this substance and a robust argument against the proposed classification can be found there.

Executive Summary

HPT 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.

HPT has been on the market in the EU since 1999 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%).

HPT as manufactured is a complex reaction mixture (UVCB-Substance) with only traces of "free" formaldehyde as placed on the market. The composition of the UVCB is driven by the ratio of the starting materials. At molar ratio of 1:1 for formaldehyde and 2-hydroxypropylamine mainly $\alpha, \alpha', \alpha''$ -trimethyl-1,3,5-triazine-1,3,5(2H,4H,6H)-triethanol (HPT) is formed. In aqueous solutions a dynamic equilibrium results whose composition depends on the concentration, pH value and temperature. Although HPT contains a maximum of 28% 'releasable' formaldehyde per molecule recent studies have demonstrated that HPT as placed on the market and used as intended contains 'free' (unbound) formaldehyde at less than 0.05% by weight. **(SMN 18537)**

In addition, measurement of ‘free’ formaldehyde at various aqueous dilutions of HPT demonstrated that the theoretical calculated maximum ‘releasable’ formaldehyde is in fact not released immediately, except at very low dilutions. Even at the lowest dilutions, the actual amount released is close to the theoretical maximum but remains significantly below the critical level of 0.1% ‘free’ formaldehyde hydrate (see Table 1). **(Hydrolysis study within dossier)** The classification proposal for HPT as a carcinogen and mutagen relies solely on the assumption of an immediate release of total ‘bound’ formaldehyde through hydrolysis under real-world conditions of use and *sufficient* released formaldehyde coming into contact with the naso-pharyngeal epithelium. Further evidence casting doubt on the relevance of the hydrolysis study included in the dossier is provided by HPT’s stability in end use fluid; the added biocide retains its efficiency for a significant period of time without the need to add additional active ingredient to the fluid being preserved (as referenced by anecdotal evidence from downstream users responsible for fluid management in metalworking shops). Given the rapid biodegradation of formaldehyde and its metabolism this is the opposite of what would be expected if all ‘bound’ formaldehyde was released immediately upon contact with water.

Table 1

Determination of “free” formaldehyde in HPT as manufactured and at commercially-relevant dilutions.		
Concentration of HPT	maximum releasable formaldehyde, (calculated)	“free” formaldehyde, (measured)
100% HPT as manufactured (UVCB-substance)	28%	<0.05% (<500ppm)*
10% HPT	2.8%	0.025%**
1% HPT	0.28%	0.0178%**
0.25% HPT	0.07%	0.01875%**
0.025% HPT	0.007%	0.00445%**
0.0025% HPT	0.0007%	0.000625%**
** Hydrolysis Study *(SMN 18537)		

Additionally HPT has a low volatility (low vapour pressure and Henry’s Law Constant) meaning that direct inhalation is not a credible means of exposure of HPT with the naso-pharyngeal epithelium.

Occupational measurements carried out with MBO, which were not included in the Competent Authority Report that was submitted to the Biocidal Product Committee, are presented in this paper. As mentioned earlier, these studies are directly relevant to HPT because both molecules are derived from the same raw materials at different ratios and act by the same mechanism of action, namely release of bound formaldehyde. These data demonstrate that MBO is relatively stable in the form in which it is “reasonably expected to be used” (i.e. its intended use) and under conditions which would potentially result in the highest exposure of humans to the non-volatile MBO i.e. through aerosolisation of an end use metalworking fluid emulsion containing MBO. The data confirms that release of formaldehyde from HPT by hydrolysis is not a simple process but instead depends on various factors in the metalworking fluid environment and that the dynamic equilibrium described for this UVCB in the dossier submitted under the Biocides Review Programme is complex.

The hydrolysis study used by the Austrian Competent Authority to justify their proposed harmonised classification of HPT as a carcinogen and mutagen, with an assumption that *sufficient* formaldehyde would be released from HPT by contact with nasal mucosa to cause an adverse toxicological event, is demonstrably not a sufficiently reliable indicator for the behaviour of HPT in the environment or in living organisms to be credible. In fact, it is evident that all ‘bound’ formaldehyde is not released instantaneously upon contact with water in the end use fluid. Instead there is a considerable weight-of-evidence is that there would be insufficient exposure (bioavailability) to MBO and therefore to HPT by the inhalation route to give scientific credibility to the classification proposal based on total releasable formaldehyde. The data presented in this paper clearly demonstrates that inhalation exposure of workers to MBO/re HPT would be below the threshold at which the RAC and all other commentators have previously concluded is necessary to cause significant toxicologically-adverse effects. This is based on its physical-chemical properties, its intended reasonable use, its relative stability in an end use fluid, and data from German Exposure Studies conducted between 2010 and 2013.

With regard to carcinogenicity in particular, there is no credible scientific evidence in the harmonisation dossier to support the proposal that HPT is a carcinogen. No carcinogenicity studies have been conducted with HPT or any other formaldehyde donor, and there is significant weight-of-evidence that HPT is not inherently carcinogen. HPT does not indicate genotoxicity in vivo following oral administration and the ambiguous results for intraperitoneal administration should not be considered due to an inappropriate application route. Additionally, quantitative Structure Activity Relationship (QSAR) analysis of the HPT 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. These data are also representative of HPT because the 3:2 substance (MBO) is known to hydrolyse to the 1:1 substance (HPT) in biological systems.

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 HPT 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 in these comments demonstrate that this is a significant oversimplification of what happens when HPT (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 a 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 and therefore also for HPT 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 most experts agree 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 HPT 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 therefore is not in accordance with the EU CLP Regulation.

I. Use and Hydrolytic Stability

HPT is an active substance which is sold in a pure form and formulated in biocidal products. It has 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 an 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 HPT. In metalworking applications, HPT is added up to 1,500 ppm final concentration in the end use fluid. It is critical to recognise that experimental data demonstrates that there is no discernible hydrolysis of HPT and therefore negligible release of 'bound' formaldehyde in the form that HPT is manufactured and placed on the market. As manufactured it has less than 0.05% (wt) formaldehyde and the available data conclusively demonstrate that HPT as placed on the market is stable.

Although laboratory based hydrolysis test data with pure water demonstrates that HPT undergoes rapid hydrolysis at high dilution, it is misleading to extrapolate this finding for classification purposes. This is because “in use” formulations are not entirely aqueous but instead consist of complex metalworking emulsions.

Additionally the free formaldehyde content within metalworking fluid concentrates containing 2% HPT has been investigated by NMR and it was demonstrated that these samples contain less than 0.01% free formaldehyde hydrate

These experiments, which were not been submitted to Competent Authorities as part of the active ingredient dossier, clearly show that HPT releases less than the critical amount of 0.1% free formaldehyde hydrate and is therefore relatively stable under conditions of normal (intended) use.

Industry experience with HPT also supports this observation since a 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 CO₂ measurements within 28 days) and can be further depleted through microbial metabolic pathways. It is therefore indisputable that if HPT at the effective dose hydrolysed immediately upon formulation to release all ‘bound’ formaldehyde then additional biocide would be required within a short space of time to maintain fluid integrity. The reason for the observation by end users that HPT is capable of providing longer-lasting antimicrobial activity in metalworking emulsions and other hydrocarbon-based solutions when used at the effective dose is not fully understood. However the fact that it does demonstrate 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 HPT with moisture.

Finally, the fact that the release of formaldehyde from HPT 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 HPT (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 HPT 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 HPT. 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 HPT 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 HPT must instead be based solely on the level of residual formaldehyde present in the substance *as placed on the market* (which is <<0.1%).

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 defines hazard classification to be based on the *inherent properties* of the substance in question. However, the proposal by the Austrian Competent Authority to classify HPT for carcinogenicity and mutagenicity solely based on total ‘releasable’ formaldehyde introduces an exposure element. This is because the proposal relies on for complete and immediate hydrolysis of HPT 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 for the substance MBO that demonstrate typical occupational exposure of workers in respect to the critical hydrolysis product formaldehyde. As mentioned in the Executive Summary exposure data generated using MBO represents the worst-case situation for exposure to HPT due to the structural similarity between these substances. The full study reports have been provided to the consultation of MBO separately and brief details of the exposure studies are given below:

Reference values for 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)

This experiment simulated the addition of MBO to a vehicle tank filled with diesel fuel in a refilling facility to approximate the exposure of employees working under these conditions to airborne formaldehyde

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

Airborne formaldehyde was measured at a production plant of *Svenska Kullagerfabriken AB* in Germany in 2010 and again in 2013.

Both types of measurement gave airborne formaldehyde values that are significantly below the WHO OEL air level of 0.4 ppm and below the AEC for formaldehyde contained in the formaldehyde core dossier (AEC 0.12 mg/m³). As MBO can be considered a “worst case scenario” in terms of formaldehyde exposure these values can also be considered to apply to HPT.

It is appropriate to consider these measured formaldehyde values that were generated during a worst-case, high energy metalworking machining operation (i.e. under normal or intended use) as part of the classification argument. This is because 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 in humans. 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 (Kuhusch et al. 2008). These data are supported by further studies conducted by Moser et al. (2005).

It is therefore demonstrably disproportionate to consider classifying HPT as a carcinogen as a means of worker protection based on a concept of total releasable formaldehyde because its release characteristics under conditions of normal use demonstrably do not support that hypothesis.

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 HPT (Priha et al. 1996). This observation adds to the weight-of-evidence that insufficient formaldehyde would be released following inhalation exposure to HPT to be available to cause toxicologically-relevant adverse effects in the nasopharyngeal epithelium.

III. Carcinogenicity

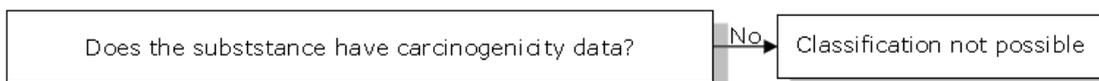
The current classification proposal is not based on the concept that HPT is inherently a carcinogen. Instead it is based on the hypothesis that human exposure to HPT liberates *sufficient* formaldehyde which is the carcinogenic component. Therefore the classification proposal is completely dependent 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.

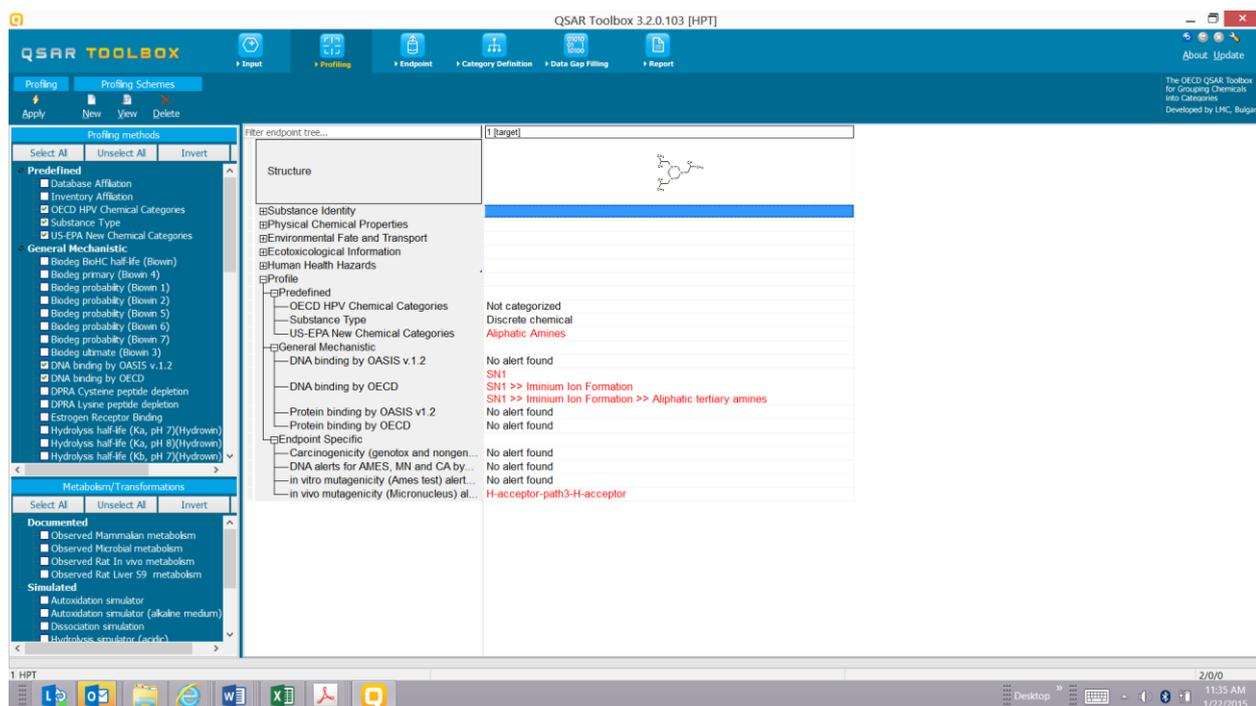
- 1) HPT as manufactured and in the form that is placed on the market contains less than 0.1% 'free' or 'unbound' formaldehyde as an impurity.
- 2) CLP states that "carcinogenic potential can be inferred from in vivo and in vitro ...mutagenicity studies". In vivo studies indicate that HPT is not genotoxic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

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.



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 tumours 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; $4.69 \cdot 10^{-9}$ 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.

IV. Mutagenicity

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 heritable 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.

V. Administrative Argument

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 HPT for the hazard classes under consideration: in other words, HPT should be classified for carcinogenicity and mutagenicity 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*. Classification should not arise from 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 from HPT by hydrolysis following contact with biological tissue.

VI. Impact of the classification as CMR (Information day)

The members of the CEFIC Formaldehyde Biocides Interest Group (FABI) invited various stakeholders including experts working for different EU Competent Authorities to an information day on formaldehyde and formaldehyde releasers in December 2014. This one-day workshop gave an 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. Slides from the workshop were submitted previously as part of our response to the public consultation on MBO.

Further Information on this topic in respect of candidate for substitution, which is only one consequence of the reclassification of HPT as a 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 to these comments.

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