Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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/A2

Adopted

30 November 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: Formaldehyde
EC number: 200-001-8
CAS number: 50-00-0

General comments

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
09/11/ 2011	United Kingdom / Daen Color UK Ltd.	p5 Table 2 : For compositions / preparations containing formaldehyde residues there should be a de minimis level of say 0.1% (1000ppm) under which it is not necessary to classify or label the preparation itself as hazardous. There is no evidence to suggest that low levels of formaldehyde per se are hazardous. The presence of formaldehyde should still be notified through Section 3 of the SDS and by country-specific OEL values as appropriate.	The CLP regulation sets rules for classification of mixtures/preparations containing dangerous substances. For most hazard classes concentration limits trigger classification of mixture/preparations only above a certain level of dangerous substance and this comment is not relevant for the present discussion.	No comment.
21/11/ 2011	Belgium/ European Trade Union Confederation	The European Trade Union Confederation supports the proposed harmonised classification and labelling for formaldehyde.	The support is noted.	The support is noted.
06/12/ 2011	Belgium/ ADVACHEM	*ECHA comment: The attachment document "Formaldehyde resins harmlessness" (Texte proposé pour le FORMACARE.doc) is copied below. Attachment No. 2.* **<u>Formaldehyde resins harmlessness</u>**	CLP regulation and criteria are hazard-based and address the intrinsic properties of substances. Considerations related to	In agreement with dossier submitter, CLP regulation and criteria are hazard-based and address

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Date: 06 December 2011 ADVACHEM S.A., route de Wallonie, darse d'Hautrage, B7334 Hautrage (Belgium) Most of the wood panels produced in Europe are agglomerated with formaldehyde based binders which remain a good compromise cost, performance and ease of use for such applications. Typically, these adhesives compositions contain a molar excess of formaldehyde. Some of this excess is released upon curing of the resin during the manufacture of the panel. However, it is well known that formaldehyde continues to be released from these panels even after the manufacturing process is completed. Concern about this problem has become a driving-force for industry to search for solutions to this problem in order to meet the standards of governmental regulations and requirements. Advachem currently produces resins with low free formaldehyde content, less than 1%, therefore these resins cannot be considered as harmful nor hazardous. These resins allow the manufacture of E1 panels (0.1 ppm in chamber test EN717-1). In case of very low emission panel is required (CARB2 and F4*), Advachem proposes a formaldehyde catcher which can be used with the resin and allows the manufacture of these types of panel. We can confirm that our products are not hazardous. The studies proposed by IARC and the French Authorities to re-classify formaldehyde as Carc. Cat 1 are based on very high level exposure tests: 1) On human volunteers: 4 hours at a concentration of 0.5 ppm with 4 peaks of 1 ppm. No evidence of carcinogenic effect in buccal celles or nasal cells was found. 2) On rats: 28 days at concentrations of up to 15 ppm. No effects were found in the local lymphoid tissues of the nose. Even no evidence of carcinogenic effects were found, IARC and the	the potential risk posed by formaldehyde-based wood panels are not relevant for the discussion. Besides, the following studies are discussed in the comment: 1) This statement seems to refer to Speit 2007. The study focus on potential detection of micronuclei in exposed volunteers. Although no effect was observed in the study, several studies detected increased incidence of micronuclei in buccal cells in different exposed populations. Besides, this study is not relevant to assess carcinogenicity as such. 2) This statement seems to refer to Kuper 2011. On the basis of this study the CLH report concludes that it tends to show that FA does no induce a proliferative effect in the nasal lymphoid tissues that could participate in haematological malignancies. Although considered in the CLH report, these two studies are not considered as key studies to either confirm or dismiss a	the intrinsic properties of substances. Considerations related to the potential risk posed by formaldehyde-based wood panels are not relevant for the discussion. The referred studies are considered in the opinion document.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		French Authorities propose the re-classification of formaldehyde. This conclusion is not logic Anyway, these levels are very high if we think that E1 level is 0.1 ppm maximum. We can also add personal opinion: After working over 25 years in formaldehyde industry, we have seen any person affected or having cancer. Therefore, in our opinion the level of formaldehyde in the panels today and the working places does not represent any hazard. The factory exists since 1995, most of the people working today have started from the beginning and there is nobody today who has any signs or symptoms of cancer. Regularly our factory has been controlled by medical local authorities. *End of attachment no. 2*	carcinogenic effect. The proposal to classify formaldehyde as carcinogenic 1A is based on the analysis of the whole and large database available on formaldehyde. Consistent evidence from the NCI cohort and from several case-control studies supported by animal data and biological plausibility shows that formaldehyde is carcinogenic at the site of contact and it is considered that these two studies do not contradict this conclusion. In particular it is noted that the Kuper study does not relate to carcinogenic effects at the site of contact.	
12/12/ 2011	Germany/ MSCA	See attached document. *ECHA Comments: The attachment DE-MSCA_Comment on Formaldehyde.doc is copied below. Attachment No. 3, General comments:* Considering the database on formaldehyde toxicology, Germany strongly supports this CLH proposal to classify formaldehyde (CAS 50-00-0) as Muta 2- H341 and Carc 1A – H351 according to CLP regulation. *End of attachment no. 3 – General Comments*	The support is noted.	The support is noted.
12/12/ 2011	Belgium/ European Panel Federation aisbl	The European Panel Federation and its national member organisations are extremely concerned by the recent proposal from ANSES on behalf of the French Competent Authorities to classify formaldehyde	The comment is noted. CLP regulation and criteria are hazard-based and address the intrinsic	The comment that there is no scientific evidence for

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		as a carcinogen Cat. 1A and mutagen Cat. 2 as this could have tremendous consequences for the production, marketing and use of all wood-based products, whereas there is no scientific evidence demonstrating the need for such a reclassification. Based on a very large amount of technical and scientific data on formaldehyde, industry has constantly worked over the years to develop a comprehensive scheme of chemical control such that the quantity of formaldehyde used for panel production and the level of exposure have been dramatically reduced. In addition, a large-scale review of the situation in the wood-based panels industry demonstrates that actually no single case of nasopharyngeal cancer has been reported in the ten thousands of workers in the wood-based panels sector using formaldehyde-based resins over the last century. Furthermore, no cases of nasopharyngeal cancer potentially linked to occupational exposure to formaldehyde have been recognised by the competent national authorities in at least 17 countries already reviewed. These findings confirm the opinion of IARC dated 15 June 2004 that nasopharyngeal cancer in humans is "a rare cancer in developed countries", where formaldehyde-based chemicals are used the most. Formaldehyde is a simple but essential organic chemical that occurs in most forms of life, including humans. At the biological level, all normally functioning cells (human, animal and vegetable) produce and metabolise formaldehyde. Due to its importance in various metabolic processes, formaldehyde is naturally present in the human body with concentrations of approximately one to two parts per million (ppm) in blood. It is an important substance in the manufacture of numerous products and is present all around us in our day-to-day lives from manmade sources and from natural sources. It neither accumulates in the human body nor in the environment because it is always rapidly oxidised or biodegraded. The general population in its living environment is exposed daily to low level of formaldehyde. In respect of indoor domestic exposure there is no scientific evidence to suggest that current domestic	properties of substances. Considerations related to the potential risk posed by formaldehyde-based wood panels are not relevant for the discussion. All epidemiological studies published to date are discussed in the CLH report without restriction to wood-based panel industry. Overall, consistent evidence from the NCI cohort and from several case-control studies supported by animal data and biological plausibility shows that formaldehyde is carcinogenic at the site of contact. The 2004 IARC's statement mentioned in the comment that nasopharyngeal cancer in humans is "a rare cancer in developed countries" refers to the baseline incidence of this cancer in the whole population and it is not in contradiction with the increased incidence of NPC detected in occupationally exposed	classification of formaldehyde as carcinogen Cat. 1A and mutagen Cat.2 is noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		exposure to formaldehyde poses a carcinogenic risk. As formaldehyde is threshold substance, scientists agree that at the low levels of indoor concentration of formaldehyde to which people are typically exposed, there is essentially no risk of cancer. In addition, the World Health Organisation very recently confirmed its recommendations for an advisory limit of concentration of formaldehyde in domestic indoor air of 0.1mg/m³ from all sources combined (at this level or below transient sensory effects may be avoided). It is important to note that the WHO publication includes a toxicological substantiation taking into account the results of the most recent IARC findings, to which to our knowledge the French proposal doesn't add any substantial new evidence. Moreover, comprehensive European indoor air studies confirm that the level of formaldehyde in homes is typically well below the WHO guideline value. The contribution of wood-based panels to this combined concentration is therefore fractional. Widely-used types of wood-based panels are commonly manufactured with the use of formaldehyde-based resins. Like all wood-based products, they emit very small amounts of formaldehyde after manufacture (among others due to the natural presence of formaldehyde in wood), the amount of which decreases quickly over time under normal conditions of use. In support of providing wood-based panels with low emissions all EPF members have pledged to produce their panel products to the lowest European formaldehyde emission classification: E1 of which the limit value is specified in European standards as well as in several Member States' regulations. The European wood-based panels industry is committed to ensuring the health and safety of workers and the protection of the environment while ensuring the quality and safety of its products. Capitalising on improving technical and scientific knowledge, the European wood-based panel industry has consistently strived for many years to enhancing the level of protection of their workers especially by reducing formaldehyde exposure to levels significantly below the regulated limits as well as to minimising the formaldehyde	population. Besides, it is noted that this IARC's statement was part of the press release announcing the decision of IARC to consider formaldehyde as a human carcinogen (http://www.iarc.fr/en/media-centre/pr/2004/pr153.html).	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		content in their products such that the quality and performance of the products produced comply with European standards and regulations. *ECHA Comment: the document: 'Formaldehyde_Response_to_ECHA.pdf' was submitted as a separate attachment. Attachment No.4 Attachment text is the same in the table.*		
14/12/ 2011	Belgium/ European Automobile Manufacturers Association.	Formaldehyde or Formaldehyde splitting off compounds are proven, safe and widely used biocidal agents in automotive industry. A classification as C 1 A carcinogen could lead to substitution processes with sub-stances where no experience regarding safe use is available. A classification as carcinogenic to humans is in practice like a ban of Formaldehyde in many areas. With regard to the absence of real alternatives and the increase of infections, e.g. in hospitals in the recent past, the proposed classification has to be balanced against the impact of a loss of Formaldehyde as biocide. As we know from various scientists (see also Report No. 47 of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, DFG [1]) no contribution to human cancer risk is expected under normal conditions of use below the given limit values (e.g. MAK or BAT). The competent Authorities in Germany (UBA - German Federal Environmental Agency and the BfR – Federal institute for risk assessment) declared in 2006 [2] that there is no danger for the health due to formaldehyde exposure even in housing spaces, if a so called "save level" is not exceeded. Even in France exists an occupational exposure limit of 0,5 ppm. Many other countries in Europe have also adopted exposure limit values for formaldehyde [3]. In our view this is not combinable with a classification as carcinogenic for humans, because for actual carcinogens is no health base limit value derivable. These publications show that the classification as C1 A carcinogen is	The comment is noted. CLP regulation and criteria are hazard-based and address the intrinsic properties of substances. Considerations related to the potential risk posed by formaldehyde are not relevant for the discussion. The statement on the reanalysis of National Cancer Institute's formaldehyde worker study seems to refer to Marsh 2010 that is further discussed in the carcinogenicity part.	The classification proposal as such does not address availability and safety of alternatives or risk management measures (incl. occupational limit concentrations). This will be done in other REACH procedures such as authorisation and restriction.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		not adequate for the properties of Formaldehyde. This is also supported by reanalysis of National Cancer Institute's formaldehyde worker study (see Literature list in the pdf file!) *ECHA Comment: The attachment: ACEA position on Formaldehyde_20111214.pdf was submitted as a separate attachment. Attachment No. 5. Attachment text is the same in the table.*		
14/12/ 2011	Malta / Malta Competition and Affairs authority.	Malta believes that the current classification of formaldehyde, that is CMR 2 under CLP, should be maintained. It is our belief that that the review of available epidemiological cohorts does not unequivocally link formaldehyde exposure to nasopharyngeal cancer and therefore it is our opinion that classification as carcinogen cat. 1A is not warranted. We are of the opinion that the basic animal and mechanistic data, which have not changed since the evaluation under the DSD, justifies only a classification to category 3 / 2(CLP).	This position is noted. To our knowledge, the European carcinogenic classification of formaldehyde has not been discussed since at the latest 1996. We agree that the experimental carcinogenicity database has not substantially changed since then but many studies have been published on mutagenicity and human carcinogenicity of formaldehyde and justify a revision of the classification of formaldehyde.	The view is noted. It should also be noted that in particular the epidemiologic studies were significantly enlarged and database on mutagenicity has significantly increased.
14/12/ 2011	Spain/ Foresa, Industrias Químicas del Noroeste, S.A.U.	To the members of the RAC, On behalf of the company Foresa, Industrias Quimicas del Noroeste, S.A.U. (a formaldehyde producer), please find below the statements issued by our Medical Service and the Social Security Mutual Society for Work-related Accidents and Illnesses, in charge of the health screening and the health care of our workers, where they certify that there is no cases of professional diseases on the records of the medical screenings made in our production plant.	The classification analysis is based on specifically-designed epidemiological studies and in absence of e.g. detailed evaluation of exposure, description of the population at stake and proper statistical analyses the certificates that have	The comment that there is no need for reclassification of formaldehyde is noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Based on this data and in our experience in the sector during almost 50 years we do not see a need of a reclassification of formaldehyde. We do thank you in advance for taking in account our position on this issue. Yours sincerely, Mrs Esther Cabrera Director *ECHA Comments: the document: FORESA position on formaldehyde reclassification proposal.zip was submitted to ECHA as a separate attachment. Attachment No. 7. There are 4 pdf files. ASEPEYO Statement for Foresa.pdf is copied below:*	been provided do not constitute a scientific element that can be included in the weight of evidence.	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		ASEPEYO MUTUA DE ACCIDENTES DE TRABAJO Y ENFERMEDADES PROFESIONALES DE LA SEGURIDAD SOCIAL N.º 151 **Vilagarcía de Arousa** Rua José Fariña Ferreño, 13 bajo 36600 Vilagarcía de Arousa (Pontevedra) Teléfono 986 56 52 52 Fax 986 51 11 66 www.asepeyo.es Don Jose Angel Lema Carou, with ID 35457527-Z, as Director of Asepeyo Villagarcia de Arosa. Hereby I certify that the company FORESA, INDUSTRIAS QUIMICAS DEL NOROESTE, S.A.U, (hereinafter "the Company"), with registered facilities in Caldas de Reis, Pontevedra (Spain) and for the period of coverage from 1st July 1993 until 31st December 2004: - has not dealt with any case of occupational disease. - there is no evidence in the records of this Entity of proceedings been initiated by affectation of nasopharyngeal cancer. The undersigned certify all statements made above, at the request of the Company, in Santiago de Compostela , on 5 of December 2011.  *End of ASEPEYO Statement for Foresa.pdf*		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		ECHA Comments: the document: FORESA position on formaldehyde reclassification proposal.zip was submitted to ECHA as a separate attachment. Attachment No. 7.FREMAP Statement for Foresa.pdf is copied below: D. JOSE MARIA LOPE SOLER, Director of FREMAP, MUTUA DE ACCIDENTES DE TRABAJO Y ENFERMEDADES PROFESIONALES DE LA SEGURIDAD SOCIAL, Nº. 61, CIF: G-28.207.017, in RUA FONTIÑAS, 43-45-47, SANTIAGO DE COMPOSTELA Hereby I **CERTIFY** that the company **FORESA, INDUSTRIAS QUÍMICAS DEL NOROESTE S.A.U** (hereinafter "the Company"), with registered facilities in Caldas de Reis, Pontevedra (Spain) and for the period of coverage from 1 January 2005 until the date of issue of the present : - Has not dealt with any case of occupational disease - There is no evidence in the records of this Entity of proceedings been initiated by affectation of nasopharyngeal cancer. The undersigned certify all statements made above, at the request of the Company, in Santiago de Compostela, on 5th of December 2011. *End of document FREMAP Statement for Foresa.pdf.* *ECHA Comments: the document: FORESA position on formaldehyde reclassification proposal.zip was submitted to ECHA as a separate*		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		attachment. Attachment No. 7. There are 4 pdf files. Medical Statement for Foresa.pdf is copied below: **Dr. María Mercedes Tilve Costas**, registered in the Official Medical College of La Coruña (Spain) with number 15/1507733, and assigned to the Occupational Health Service of the company FORESA, Industrias Químicas del Noroeste, S.A.U. (hereinafter "the Company"), a formaldehyde production plant located in Avenida de Doña Urraca, 36650 Caldas de Reis, Pontevedra (SPAIN), **CERTIFIES**: According to the data in the files of the Occupational Health Service of the Company, and since the Company was founded in 1964: - there is not recorded any occupational disease with pathology associated with exposure to the formaldehyde, and - there is no evidence that any employee of the Company had been diagnosed with nasopharyngeal cancer. - do not figure in any case of occupational disease related to this or any other diagnosis. In witness whereof, and for such purposes as may arise, this certification is issued in Caldas de Reis, Pontevedra, 9th of December 2011.  Dr. María Mercedes Tilve Costas Doctor nº 15/1507733 Official Medical College of La Coruña (Spain) *End of document Medical Statement for Foresa.pdf.*		
14/12/ 2011	Portugal/ BRESFOR, Industria do Formol, S.A.	To the members of the RAC, On behalf of the company BRESFOR, Industria do formol, S.A. (a formaldehyde manufacturer), please find below the statements issued by our Medical Service, in charge of the health screening and the health care of our workers, where he certifies that there is no cases	The classification analysis is based on specifically-designed epidemiological studies and in absence of e.g. detailed evaluation of exposure, description of the	The comment that there is no need for reclassification of formaldehyde is noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		of professional diseases on the records of the medical screenings made in our production plant. Based on this data and in our experience in the sector during 38 years we do not see a need of a reclassification of formaldehyde. We do thank you in advance for taking in account our position on this issue. Yours sincerely, Mr Rui Pereira da Costa Director *ECHA Comments: the document: BRESFOR position.zip was submitted as a separate document. Attachment No.8 consist of 2 documents. BRESFOR position.pdf is the same in the table.* *Medical statement BRESFOR.pdf is copied below:*	population at stake and proper statistical analyses the certificates that have been provided do not constitute a scientific element that can be included in the weight of evidence.	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Dr. Fernando Jorge Almeida de Mautempo Coelho, registered in the Portuguese Medical Association, North Regional Section with number 27997, and assigned to the Occupational Health Service of the company BRESFOR, Indústria do Formol S.A. (hereinafter "the Company"), a formaldehyde production plant located in Avenida dos Bacalhoeiros, Apartado 13, 3834-908 Gafanha da Nazaré (Portugal), CERTIFIES: According to the data in the files of the Occupational Health Service of the Company, and since the Company was founded in 1973: - there is not recorded any occupational disease with pathology associated with exposure to the formaldehyde, and - there is no evidence that any employee of the Company had been diagnosed with nasopharyngeal cancer. - do not figure in any case of occupational disease related to this or any other diagnosis. In witness whereof, and for such purposes as may arise, this certification is issued in Gafanha da Nazaré, 12th of December 2011.  Dr. Fernando Jorge Mautempo Doctor nº 27997 Portuguese Medical Association *End of attachment no. 8 : Medical statement BRESFOR.pdf*		
14/12/ 2011	United States/ American Chemistry Council	Given the imminent release of the NCI update for NPC and the questions raised in the scientific literature, no classification decision should move forward without considering the soon to be submitted NCI update of the NCI cohort. Therefore, ACC concludes that ECHA	It is not known when and if such an update will be published. In the meantime, the available	On behalf of RAC ECHA contacted NCI to receive the outstanding update

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		should maintain the existing classification, cat 2 or cat. 3 DSD.	database is considered as sufficiently robust so that a conclusion can be adopted.	on nasopharyngeal tumours as soon as possible. However waiting for new data will not postpone the timelines for decision in RAC.
15/12/ 2011	Austria/ Allgemeine Unfallversiche-rungsanstalt	We strongly support the "Resulting harmonised classification" Muta 2 – H341 and Carc. 1A – H350 for formaldehyde. Known Toxicologist end up with the same resulting classification concerning the properties of formaldehyde as can be seen within the CLH-report. e.g.: Formaldehyde is also listed in the 12th Report on Carcinogens published by the U.S. Department of Health and Human Services. (http://ntp.niehs.nih.gov/?objectid=035E57E7-BDD9-2D9B-AFB9D1CADC8D09C1) This report includes 54 profiles for substances listed as known to be human carcinogens and Formaldehyde is one of them. Unfortunately adding Formaldehyde into this list took years of debates. There is also a so called "historic" breakthrough in controlling formaldehyde in woodworking industries that forces employers to reduce exposure as much as technical possible. Unfortunately this joint declaration does not seem to be known in big parts of the Austrian (woodworking) industry. Nevertheless it shows the concerns handling this chemical. http://www.wbpionline.com/news/fullstory.php/aid/875/Historic_agreement_within_European_woodworking_industries.html The Austrian list of occupational diseases does not specially refer to formaldehyde like it does concerning Plumb or Benzene. Thus statistics of the Allgemeine Unfallversicherungsanstalt (Austrian Workers' Compensation Board) often miss work-related cancer directly caused by formaldehyde.	The support is noted.	The comment is noted.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON FORMALDEHYDE

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
15/12/ 2011	Poland/ MSCA	Acceptable is following labelling: Acute Tox. 3 – H331 Acute Tox. 3 – H311 Acute Tox. 3 – H301 Skin Corr. 1B – H314 (SCL: Skin Corr 1B 25%, 5%≤ Skin Irrit 2/Eye Irrit 2<25%, STOT SE 3- H335 ≥5%) Skin Sens. 1 – H317 (SCL of 0.2%) [STOT SE 3 – H335] Muta 2 – H341 Doubts: Carc 1A	The position is noted.	The position is noted. Other endpoints than carcinogenicity and mutagenicity were not discussed for classification purposes.
15/12/ 2011	Germany/ TEGEWA	page 18 2.2 Identified uses Current text: "General public: detergents, disinfectants and cleaning agents, building and insulating material, paints and lacquers, adhesives, preservative in cosmetics." Recommendation: Please add: "exposure to hydrolyzed or released formaldehyde from finished textiles and leather goods". The respective standards are: ISO-Standard ISO 14184, Textiles -- Determination of formaldehyde -- Part 1: Free and hydrolysed formaldehyde (water extraction method) ISO-Standard ISO 14184, Textiles -- Determination of formaldehyde -- Part 2: Released formaldehyde (vapour absorption method) EN ISO standard 17226-3:2011 Leather - Chemical determination of formaldehyde content - Part 3: Determination of formaldehyde emissions from leather (ISO 17226-3:2011); 2)page 19 4.1 toxicokinetics Current text: "From in vitro experiments using human skin, it is estimated that the absorption of a concentrated solution of formalin through the skin amounted to 319 µg/cm2 per hour." NTP statement:	Identified uses: Thank you for the information. The identified uses included in the CLH report are not intended to be an exhaustive list of formaldehyde uses and the additional information is not considered to have an impact on the classification analysis. Toxicokinetics: we agree that absorption of formaldehyde by dermal route is low. This is in line with the information given in the CLH report related to the *in vitro* rate of absorption of 319 µg/cm² per hour (quoted from the IARC monograph, 2006). The recommended information is not added in the CLH report as it is not considered to have an impact on the classification	Noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		"Although formaldehyde is rapidly and almost completely absorbed from the respiratory or gastrointestinal tracts, it is poorly absorbed from intact skin. (NTP 2010, page XV) No tumors were observed in the skin-painting study in mice.(NTP 2010, page 273)." Reference: NTP. 2010. Report on Carcinogens Background Document for Formaldehyde. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/twelfth/2009/November/Formaldehyde_BD_Final.pdf. Recommendation: Please add "Although formaldehyde is rapidly and almost completely absorbed from the respiratory or gastrointestinal tracts, it is poorly absorbed from intact skin."	analysis.	
15/12/ 2011	United Kingdom/ Lonza Swizerland	This submission responds to the call for comments on the French CLH report on formaldehyde (dated 28 September 2011). Lonza's assessment is that the proposed harmonised classification is inappropriate. This submission seeks to bring to the attention of the RAC significant systemic flaws in the approach taken in the CLH report. Lonza wishes to comment on one aspect of this proposal: a) Carc. Cat. 1; R45 (category 1A carcinogen) Lonza considers that the carcinogenicity classification is not supported by the evidence. Accordingly, Lonza proposes, that the correct classification for the substance is: CArc. Category 2 (CLP)(Page 2 of attached document). *ECHA Comment: the document: 'Lonza_Formaldehyde_Comments_111215.doc' was submitted as a separate attachment. Attachment No.11. Page 2 is copied below.*	The position is noted.	The comment is noted.

<table>
<tr><th>Date</th><th>Country / Organisation/ MSCA</th><th>Comment</th><th>Dossier submitter's response to comment</th><th>RAC's response to comment</th></tr>
<tr><td></td><td></td><td>

<u>INTRODUCTION</u>

A large amount of new relevant data on carcinogenicity and on mutagenicity of formaldehyde has been published in the past 15 years that has not been evaluated by the TC C&L.

The French Competent Authorities considers that the classification for carcinogenicity and mutagenicity needs to be revised on the basis of the new studies available.

Carcinogenicity and mutagenicity as other CMR properties justifies a harmonised classification and labelling according to article 36 of CLP.

<table>
<tr><th>Proposed classification based on Directive 67/548/EEC criteria:</th><th>Proposed classification based on CLP criteria:</th></tr>
<tr><td>T; R23/24/25
Muta Cat 3; R68
Carc. Cat. 1; R45</td><td>Hazard statements:
Acute Tox 3 – H331
Acute Tox 3 – H311
Acute Tox 3 – H301

Skin Corr 1B – H314
Skin Sens 1 – H317
STOT RE 1 – H335
Muta Cat 2 – H341
Carc 1A – H350</td></tr>
</table>

Overview

This submission responds to the call for comments on the French CLH report on formaldehyde (dated 28 September 2011). Lonza's assessment is that the proposed harmonised classification is inappropriate. This submission seeks to bring to the attention of the RAC significant systemic flaws in the approach taken in the CLH report.

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<table>
<tr><th>Date</th><th>Country / Organisation/ MSCA</th><th>Comment</th><th>Dossier submitter's response to comment</th><th>RAC's response to comment</th></tr>
<tr><td></td><td></td><td>Lonza wishes to comment on one aspect of this proposal:

a) Carc. Cat. 1; R45 (category 1A carcinogen)

Lonza considers that the carcinogenicity classification is not supported by the evidence.

Accordingly, Lonza proposes, that the correct classification for the substance is:

<table><tr><th>Proposed classification based on Directive 67/548/EEC criteria:

• Carc Cat 3; R40</th><th>Proposed classification based on CLP criteria:

Carc. Category 2</th></tr></table>
End of page 2 of attachment no. 11</td><td></td><td></td></tr>
<tr><td>15/12/ 2011</td><td>Sweden/ MSCA</td><td>SE supports classification of Formaldehyde (Cas No 50-00-0) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations.

The Swedish Chemicals Agency – KemI (Swedish CA for REACH and CLP) recognizes that the French Competent Authority has provided a thorough, feasible and well referenced CHL report for Formaldehyde, especially considering all the old and new data on carcinogenicity and mutagenicity of formaldehyde that now has been evaluated.</td><td>The support is noted.</td><td>The position is noted.</td></tr>
<tr><td>15/12/ 2011</td><td>Portugal/ APEQ-Portuguese Chemicals Association</td><td>Please see the Zip file named APEQ TECHNICAL NOTE 013 2011.pdf

ECHA Comment: the document 'FORMALDEHYDE RESPONSE.zip' was submitted as a separate attachment. Attachment No.12. APEQ TECHNICAL NOTE 013 2011.pdf is copied below.</td><td>The information is noted.</td><td>Noted.</td></tr>
</table>

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		ECHA PUBLIC CONSULTATION ON THE CLH REPORT **Proposal for Harmonised Classification and Labelling** **Based on Regulation (EC) No 1272/2008 (CLP Regulation),** **Annex VI, Part 2** **Substance Name: FORMALDEHYDE** **CAS Number: 50-00-0** **EC Number: 200-001-8** **APEQ POSITION** APEQ, the Portuguese Association of Chemical Companies, aiming constructively cooperate with the RCA - Committee for Risk Assessment of the REACH Regulation and with ECHA, presents a study which full reflects the position of the Association and their Members, producers of this substance for a long time.. 1. SCOPE In compliance with the provisions of REACH - "Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals" No 1907/2006, and the provisions of CLP Regulation No 1272/2008, RAC will limit its assessment to the hazard classes for which classification will be proposed. Information only relevant for the classification for other hazard classes must be submitted. However, RAC may consider another category more appropriate for the classification of the substance after having exanimate the available information. So we have been invited to submit comments and additional information we hold, but as we support a different classification from the classification proposed by France, Apeq presents in the Annexe I his response and another classification. 2. PETITION Through our European Association, FORMACRE – Formaldehyde Sector Group of CEFIC, where APEQ sits in some Board of Directors, we kindly ask you that our experts seat, as observers in your RAC meeting, when this file will be under discussion. We remain at your disposal to clarify any other question.		

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		With consideration , *Lubélia Nogueira Penedo* Director General - APEQ lpenedo@apequimica.pt Lisbon, 2011 – 12 - 15 *End of attachment no. 12 (APEQ TECHNICAL NOTE 013 2011.pdf)*		
15/12/ 2011	Portugal/ APEQ- Portuguese Chemicals Association	Medical Declaration stating the good health of one formaldehyde plant workers. See attached file at the end. *ECHA Comment: the document: 'APEQ Medical Declaration.doc' was submitted as a separate attachment. Attachment No.13 is copied below and the embedded document 'Medical CEMETRA Declaration.pdf' in Portuguese is not copied :* **ECHA PUBLIC CONSULTATION ON THE CLH REPORT** **Proposal for Harmonised Classification and Labelling** **Based on Regulation (EC) No 1272/2008 (CLP Regulation),** **Annex VI, Part 2** **Substance Name: FORMALDEHYDE** **CAS Number: 50-00-0** **EC Number: 200-001-8** **APEQ ASSOCIATED MEMBERS POSITION** Dear Sirs, Regarding the public consultation on the re-classification and labeling of Formaldehyde (n.º CAS 50-00-0 and CE n.º 200-001-8), this	The classification analysis is based on specifically-designed epidemiological studies and in absence of e.g. detailed evaluation of exposure, description of the population at stake and proper statistical analyses the certificates that have been provided do not constitute a scientific element that can be included in the weight of evidence.	The statement is noted.

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		Association would like to add to our previous position the following: 1. The APEQ - Portuguese Association of Chemical Companies is an association created in 1994, which associates Portuguese chemical companies, with the aim of contributing to the restructuring and rmaximization of business interventions and collaboration with national and european authorities, regarding the establishment of legislative fair measures concerning the sector, with special emphasis on sustainable development and continuous improvement of health, environment, and process and products safety; 2. Portugal has companies producing Formaldehyde since 70's decade; 3. According to the annexed Medical Declaration from the Labor and Occupational Health Department concerning workers'health evaluation, there is no evidence that the formaldehyde occupational have caused diseases, namely nasopharyngeal cancer.  Medical CEMETRA Declaration.pdf We remain at your disposal to clarify any other question. With consideration,		

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		Lubélia Nogueira Penedo Director General - APEQ lpenedo@apequimica.pt Lisbon, 2011 – 12 - 15 *End of attachment no. 13 , not included embedded Portuguese document .*		
20/12/ 2011	France/ Women in Europe for a Common Future	*ECHA Comment: Due to technical problem after ECHA launched new web site on 15 December 2011, the'Give Comments' link was active and this comment was received.* *Attachment no. 14 'WECF formaldehyde consultation.pdf' has the same content.* WECF (Women in Europe for a Common Future) has been working on chemicals and health issues, especially children's health for years and formaldehyde is one of the substances that triggered a huge interest in its health and environment activities. In November 2011, WECF tests of wooden toys bought in France, Germany and the Netherlands confirmed the presence of formaldehyde in wooden toys for children under 3. Formaldehyde is omnipresent in indoor environments: Conclusions p.18: "Formaldehyde is extensively produced industrially worldwide for use in the manufacture of resins, as a disinfectant and fixative, or as a preservative in consumer products. Finally, it should be noted that secondary formation of formaldehyde occurs in air through the oxidation of volatile organic compounds (VOCs) and reactions between ozone (mainly from outdoors) and alkenes (especially terpenes). " "Prevalence of formaldehyde in many consumer products, resulting in a substantial presence of formaldehyde in indoor environments: furniture and wooden products containing formaldehyde-based resins such as particleboard, plywood and medium-density fibreboard; insulating materials, textiles; do-it-yourself products such as paints, wallpapers, glues, adhesives, varnishes and lacquers; household	The information is noted. It is not clear to which document the page references relate to. However, classification discussion is hazard-based and the additional information provided on exposure and uses are not considered to have an impact on the classification analysis. Besides, the current classification dossier focus on carcinogenicity and mutagenicity of formaldehyde and sensitisation is not addressed.	Noted.

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		cleaning products such as detergents, disinfectants, softeners, carpet cleaners and shoe products; cosmetics such as liquid soaps, shampoos, nail varnishes and nail hardeners; electronic equipment, including computers and photocopiers; and other consumer items such as insecticides and paper products." Source: http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf Children are especially vulnerable to indoor air pollution and formaldehyde is present in high concentrations in children's indoor environments: Conclusions page 18: « Air quality measures evidence much higher concentrations of formaldehyde in indoor than outdoor environments (10 fold compared to outdoor) whether in private housings, schools, offices, etc. Medium indoor concentrations are around 20 micrograms/m3 whereas they often reach a maximum of 4,5 micrograms/m3 in outdoor environments" Source : La pollution intérieure dans les écoles, Mémoire de Fin d'Etudes présenté par Keijzer Marie-Noëlle en vue de l'obtention du grade académique de Master en Sciences et Gestion de l'Environnement Année Académique: 2008-2009, Université Libre de Bruxelles Institut de Gestion de l'Environnement et d'Aménagement du Territoire Faculté des Sciences. Conclusions page 18: According to WHO European region, asthma and rhinoconjunctivitis symptoms cause a significant burden of disease and that the prevalence of both is rising in European children. Allergic and asthmatic symptoms are associated with, among other things, indoor and outdoor air quality. In 1999–2004, asthma prevalence in children across the European study centres varied from less than 5% to over 20%. source: http://www.euro.who.int/__data/assets/pdf_file/0012/96996/3.1.pdf Conclusions page 18: "In rooms containing much furniture made of chipboard, significantly higher formaldehyde levels were detected on average than in rooms with little or no such furniture. Average		

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		hexanal levels were significantly higher in rooms whose chipboard furniture was bought after the limitation of formaldehyde emissions from chipboard was introduced." "Formaldehyd ist der Aldehyd in der Raumluft mit der höchsten mittleren Konzentration (23,3 µg/m3)." source : Kinder-Umwelt-Survey (KUS) 2003/06 Innenraumluft – Flüchtige organische Verbindungen in der Innenraumluft in Haushalten mit Kindern in Deutschland, Umweltbundesamt, August 2010, http://www.umweltdaten.de/publikationen/fpdf-l/4011.pdf Action at community level is required: Conclusions page 13: "Clean indoor air is essential for the health of the population as a whole, and even more important for vulnerable groups like infants, children and the elderly, or people already suffering from chronic diseases, such as respiratory or allergic disorders," said Mrs Androulla Vassiliou, European Commissioner for Health. "The European Commission, in close cooperation with the WHO Regional Office for Europe, supports the development of specific guidance for indoor spaces. Targeted action might also be needed to avoid hazardous exposures, particularly in schools or other places where children spend their time." Source: Speech during 28/01/2009 Press release WHO Luxemburg meeting (January 28, 2009). http://www.eurosafe.eu.com/csi/eurosafe2006.nsf/wwwVwContent/4B7366AAF07B5A71C125754E003CE02A?opendocument&context=546FDA82B09D2691C12571AE0049DB2B Conclusion page 13 : At Community level, the INDEX project states in its conclusions that "Wantke et al. (1996) reported that formaldehyde-specific IgE and respiratory symptoms were reduced when children transferred from schools with formaldehyde concentrations of 53 to 92 µg/m3 (43 to 75 ppb) to schools with concentrations of 28 to 36 µg/m3 (23 to 29 ppb). Garrett et al. (1999) reported increased sensitization associated with the formaldehyde level in children's homes which had a median value of 15.8 µg/m3 (12.6 ppb)."		

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		"Because of its high chemical reactivity, formaldehyde is the most important sensory irritant among the chemicals assessed in the present report. Due to its ubiquitousness in indoor environments and to the increasing evidence indicating that children may be more sensitive to formaldehyde respiratory toxicity than adults, it is considered a chemical of concern at levels exceeding 1 µg/m3 […]". Source: Final report, The INDEX project Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU, European Commission Directorate-General Joint Research Centre, 2005 Conclusions page 13: action at community level would be complementary to CEHAPE (Children's Environment and Health Action Plan for Europe) regional priority goal III which aims among others at " (d) applying and enforcing regulations to improve indoor air quality, especially in housing - child care centres and schools, with particular reference to construction and furnishing - materials"; source: http://www.euro.who.int/__data/assets/pdf_file/0006/78639/E83338.pdf		
21/12/ 2011	Sweden/ ChemSec	*ECHA Comment: Due to technical problem after ECHA launched new web site on 15 December 2011, the'Give Comments' link was active and this comment was received.* Considering the solid evidence collected by France of the carcinogenic and mutagenic properties of Formaldehyde, we fully support the change of classification of Formaldehyde to carcinogenic 1A and mutagenic 2.	The support is noted.	The support is noted.

Carcinogenicity

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON FORMALDEHYDE

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
21/11/ 2011	Belgium/ European Trade Union Confederation	Formaldehyde has been recognised as a human carcinogen by IARC in 2006. Formaldehyde is included in the Trade Union Priority List for REACH authorisation (http://www.etuc.org/a/6023) as a human carcinogen.	Noted.	The information is noted.
28/11/ 2011	United Kingdom / Individual	Why does the UK government allow the use of artificial sweeteners in products in this country which are known to contain Formaldehyde which is linked to Carcinogenic tumours in humans? Surely this is not in the interest of good public health and can only benefit the chemical companies that manufacture the substance.	This comment is not relevant for the classification discussion.	Noted.
06/12/ 2011	Germany/ Individual	see attached document *ECHA comment: Attached document "Comments on the CLH Report for Formaldehyde" (FA_CLH.pdf) is attached separately. Attachment No. 1 See Mutagenicity, page 45 in this table.*	This comment is fully presented and discussed in the mutagenicity part below. Please see RCOM below.	Noted.
12/12/ 2011	Germany/ MSCA	See attached document *ECHA Comments: The attachment 'DE-MSCA_Comment on Formaldehyde.doc' section Carcinogenicity is copied below. Attachment No.3, Section Carcinogenicity* **Carcinogenicity:** Page 10/11: The scientific justification for the proposal to classify in Carc Cat 1 may be considered to be further substantiated by the available epidemiological evidence for systemic cancer. A relationship between exposure to formaldehyde and haematopoetic malignancies, especially myeloid leukaemia, was observed in independent epidemiological studies. When taking into account the level of exposure to formaldehyde meta-analysis confirmed the association (Zhang et al., 2009), in line with reports on lymphatic cell genotoxicity and bone marrow toxicity in highly exposed humans. Page 158, concerning evidence of a carcinogenic effect	Page 10/11: we consider that the level of evidence for leukaemia is less robust than for nasopharyngeal cancer considering that indications of genotoxicity in lymphocytes in humans is not confirmed in animals, absence of robust evidence of an effect of FA on bone marrow and limitations in the biological plausibility for systemic carcinogenicity of FA. Page 158, concerning evidence of a carcinogenic effect of formaldehyde via the oral route: induction of micronuclei in the gastro-intestinal tract (Migliore 1989) is acknowledged as presented and discussed in the mutagenicity part of the CLH report. Induction of tumours in the gastrointestinal tract was however not observed in the	Noted, the view of the DS is supported (see opinion document, text on this reference). The database for the oral route is not sufficient to conclude on the

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		of formaldehyde via the oral route: When concluding the overall evidence, it might also be considered that single gavage application of 200 mg/kg bw formaldehyde in aqueous solution to rats produced increases in micronuclei and other nuclear abnormalities in the epithelial cells of the stomach, duodenum, ileum and colon (Migliore et al., 1989). Intermittent dosing at higher levels might in principle produce other results than chronic dosing at a lower dose of the corrosive substance. Page 159, 3rd para concerning tumours at distant sites: It should be taken into account that tissue relevant for haematopoetic cancers has not been evaluated comprehensively and high incidences in nasal tumours (and mortality) in the rat may mask, to some degree, effects at other sites.	carcinogenicity studies Til 1989 and in Tobe 1989. In Takahashi 1986, the increase in squamous cell papillomas in the forestomach exposed for only 32 weeks is therefore considered equivoqual and overall, we consider that no convincing evidence shows a carcinogenic effect of formaldehyde via oral route. Page 159, 3rd para concerning tumours at distant sites: Noted. Besides, some of the carcinogenicity studies by inhalation focused on the nasal cavity and a full histopathological analysis of all tissues was not performed (Monticello 1996, Feron 1998, Woutersen 1989). Page 160, concerning overall conclusion: Noted Page 164 Table Myeloid Leukaemia: the study by Pinkerton 2004 is included in the table but is referred as the NIOSH cohort. Page 166f: the updated analyses of mortality of Hauptmann 2003/2004 considering the additional deaths as published in Beane-Freeman 2009 and Marsh 2010 have been added in the revised CLH report for the sake of comprehensiveness. It is noted that updated analyses were provided for lympho-haematopoietic malignancies but not for the different solid cancers. However, as the explanation of why	carcinogenic potential for this route. Has been considered. Noted. Noted.

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		Page 160, concerning overall conclusion: Effects at distant sites may be considered to have not been investigated sufficiently. Page 164 Table Myeloid Leukaemia: Positive results by Pinkerton 2004 (follow-up of Stayner) should also be taken into account. Page 166f: Regarding the analysis of the NCI cohort by Hauptmann et al. (2004), it may be noticed that Beane-Freeman et al. (2009) found 1006 additional death in the period from 1980 to 1994 when accessing the National Death Index. Such findings are not uncommon for large cohort studies. As there is no indication that data drop-outs were selective. Thus the analysis of Hauptmann et al. (2004) should be regarded to remain valid unless the opposite is demonstrated. Recently, it has been claimed by Marsh et al. (2010)[1], that a correction of the results from Hauptmann et al. (2004) is warranted. We would not agree that such update is necessary before decisions can be taken, although such re-analysis should provide valuable information.	these cases were not initially included is not linked to a change in the criteria for inclusion, it is not expected to create a bias of analysis and we agree that the results of Hauptmann 2004 are valid. Page 170, 1st paragraph starting "Overall…": The meta-analysis by Zhang (2009b) do not analyse separately the results from industrial and professional populations and do not allow to confirm or invalidate a potential discrepancy between the two. Discrepancy may be explained by differences in exposure levels but a biais specific to occupational populations may also be hypothetised. Besides, the final conclusion that the level of evidence for induction of leukaemia is lower that for NPC is not only based on the discrepancy in the epidemiological results but also on the absence of convincing evidence of an effect of formaldehyde at distant sites and absence of support from robust animal carcinogenicity studies. Page 172, 2nd paragraph starting "*At the site of contact …*": Noted Page 173, 4th paragraph starting "Besides": The mechanism that leads to lower EC3 after repeated exposure	Noted, the uncertainty from additional deaths with regard to NPC are considered in the weight of evidence analysis. No further comment.

[1] Marsh GM, Youk AO, Morfeld P, Collins JJ, Symons JM. 2010, Incomplete follow-up in the National Cancer Institute's formaldehyde worker study and the impact on subsequent reanalyses and causal evaluations Reg. Tox. Pharmacol. 58, 233-236

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		Page 170, 1st paragraph starting "Overall…": A discrepancy between results for professionals vs. industry workers would not discredit any positive findings as shown in the meta-analysis by Zhang et al. (2009). Reflecting the hypothesis tested, the authors excluded studies which lacked a clearly exposed group, included only the highest exposed groups when studies differentiated levels of exposure and selected the dose metrics when more than one was used (e.g. peak exposure preferred over average exposure intensity etc.). This meta-analysis provides evidence of an association of peak formaldehyde exposure with leukaemia, particularly of the myeloid type. Differences in exposure levels and peak exposures between "professionals" and "industry workers" may exist. Page 172, 2nd paragraph starting "*At the site of contact …*": Grouping of cases in plant 1 of the NCI cohort does not lower the level of evidence as a plausible explanation for this clustering has been provided in the same paragraph.	to formaldehyde may not been fully known. It probably involves local reactions and do not constitute an evidence of a systemic effect of formaldehyde. The study by Neuss (2010b) did not find induction of DPX in cells in contact with previously FA-exposed cells and tend to show that FA is not released from cells to cells. Page 173 concerning the study by Zhang et al. (2010): The identification of cytogenic changes by Zhang 2010 is considered in the evaluation, but this result is based on a very low number of subjects (10) and is also limited by the pooled analysis of the samples. A difference in the growth kinetic of each clone may therefore have interfered with quantification. These results therefore need to be replicated to provide an evidence of an effect. Page 174 concerning the study by Lu et al. (2010, 2011): Noted. Page 175 (Zhang 2010): The lower level of white blood cell counts were in the normal range values and such effect was not reported in experimental animals so that the effect observed in Zhang 2010 need to be confirmed. Section 4.10.5 p. 173 ff, Cancers at distant sites: Although the understanding or confirmation of a	Page 172, 2nd Sharing the view of the DS is noted. Page 173, 4th paragraph starting "Besides": Rapporteurs agree with DS: Lymph node cell numbers were increased at two highest concentrations (without a clear dose-concentration response at lower

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		Page 173, 4th paragraph starting "Besides": Formaldehyde can form various adducts and metabolites, some of which can release formaldehyde. The measurement method used was not suitable to assess the situation in blood at the required level of complexity. Please refer to our comments made on the toxicokinetics section. Interestingly, there is some evidence for accumulation of adducts from skin sensitisation study in mice: After repeated exposure (14 days in approx. 2 months) of dosages below the sensitising threshold (EC_3) an EC_3-exceeding SI was observed (de Jong et al. 2007)[2]. This may suggest that accumulation of toxicologically relevant formaldehyde adducts / reaction products / metabolites is required to detect certain responses. Page 173 concerning the study by Zhang et al. (2010): Although monosomy of chromosome 7 and trisomy of chromosome 8 were also observed in controls the differences are highly significant and are to be regarded as effect. This study provides data on highly exposed workers with concomitantly determined individual levels of exposure (in contrast to other studies). The meaning of these cytogenetic anomalies may not be known concerning the molecular oncogenesis but are associated with the prognosis of AML and, hence, may	mechanism of action is not a prerequisite for classification, we consider that the biological plausibility of the effect should be taken into account in the weight of evidence to reach a potential conclusion of a causal relationship between a chemical substance and a cancer. For induction of formaldehyde-induced tumours of the lympho-haematopoietic system, the absence of effect in experimental animals and of robust evidence of a systemic effect of formaldehyde does not support the biological plausibility of this type of cancer and the level of evidence for induction of leukaemia is considered lower than for nasopharygeal cancer. Section 4.10.5 page 173 ff (also relevant for section 1.3 on page 6 and section 4.10.6 on page 176/177): the possibility to set SCL is discussed at the end of the section 4.10.6 of the CLH report. The use of human data to set SCL is not recommended in the guidance due to difficulties in establishing a reliable dose-response curve. Experimental data could be used according to the T25 approach but the guidance states that determination of T25 may not be possible in the case of a non-systemic contact carcinogen. Criteria for SCL compare T25 with doses in mg/kg bw/d and	concentrations). Increased SI stimulation index in cell suspensions at lower concentrations after repeated exposures compared to single exposure does not indicate accumulation of adducts in lymph nodes. Page 173 concerning the study by Zhang et al. (2010): Study has adequately been reflected on in the dossier by DS. Page 174

[2] De Jong WH, Klerk AD, Beek MT, Veenman C, Van Loveren H (2007) Effect of prolongeated exposure to formaldehyde donors wih doses below the EC3 value on draining Lymph node responses. Journal of Immunotoxicology 4: 239-246

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		play a role in the development of AML. However, the observed potential haematotoxicity is an additional important indication concerning the effect of formaldehyde on the haematopoetic system. Page 174 concerning the study by Lu et al. (2010, 2011): Exposure in these studies was limited to single (6h) or short-term exposure (6h x 5d). Page 175 (Zhang 2010): Although the decrease in leucocytes was without clinical significance it may indicate a relevant effect. Section 4.10.5 p. 173 ff, Cancers at distant sites: Potential mechanisms to explain cancers at distant sites (leukaemia, myeloid leukaemia) have been postulated and could, so far, neither be confirmed nor disproved convincingly. Therefore, the reported epidemiologic evidence for association of formaldehyde exposure and distant site cancer in highly exposed professional should not be dismissed. This information could, according to CLP Guidance chapter 3.6.2.3.2 be used for "additional considerations" (multi-site response), supporting the proposal for classification as Carc 1A. In this context it is noted that "additional consideration" on the mode of action, taking into account the role of growth stimulation due to cytotoxicity, should not lead to a	categorisation according to inhalation doses is not proposed. In this case, the guidance proposes to convert air concentration of a carcinogen into a dose in mg/kg bw/d using a default conversion value. But the relevance of such an approach for a local carcinogen by inhalation is unclear and on this basis we do not propose to set SCL. It is however noted that if such an approach is applied, the studies by Kerns 1983 and Monticello 1996 are considered as the most robust studies to establish T25 considering the relevant exposure duration, high number of animals per group and reduced dose spacing around T25. By interpolation of the tumour incidence at the two highest doses, both studies indicates similar T25 values of 10.40 ppm (Kerns 1983) and 10.60 ppm (Monticello 1996). The studies by Kamata 1997 and Sellakumar 1985 are considered less robust due to more important dose spacing and lower number of animals (Kamata 1997) but they indicate T25 in the same range around 10 ppm. The studies By Holmström 1989, Feron 1989 and Woutersen 1989 were not considered relevant mainly because of absence of induction of tumours (Woutersen 1989, Holmström 1989) or limited duration of exposure (Feron 1989). A T25 of 10 ppm is equivalent for male rats to 0.63 mg/kg bw/d according to the conversion factor in the guidance and corresponds to a high potency.	concerning the study by Lu et al. (2010, 2011): Noted. No further comment. DS's view agreed. It is to be noted that the available data in animals do not give indications, however the database is not sufficient to draw a firm conclusion.

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		classification in Cat 2 rather than Cat 1. Considering the mutagenicity of the compound, the mechanism of tumour induction should not be regarded to be secondary (instead, efficient repair at low exposure reduces tumour incidence below the practical limit of detection). Taken together the data presented in the CLH dossier as well as the comments presented here, we consider it necessary to examine whether epidemiological findings regarding tumours at distant sites (leukaemia) should be taken into account to support the classification of carcinogenicity Cat 1A. <u>Section 4.10.5 page 173 ff (also relevant for section 1.3 on page 6 and section 4.10.6 on page 176/177):</u> The EU has adopted the T25 concept for carcinogenicity (Dybing et al., 1997)[3] with additional considerations as a measure for potency and developed a guidance document (EC, 1999) to assist in establishing SCLs for carcinogens, based on potency categories. By using this approach the SCL may be reduced or occasionally raised from the default generic concentration limits. This concept is also included in the CLP guidance. With respect to the data background of formaldehyde we consider it necessary to examine whether formaldehyde can be categorised according to the T25 approach.	Several elements may modify the preliminary evaluation of the T25: - dose-response relationships: the consistency of the results between the different studies gives a good confidence in the estimated T25. However, it is noted that no tumour is induced at 2 ppm or lower doses and at doses lower than the T25 a lower potency is expected. - Site/species/strain/gender activity: the carcinogenic activity of formaldehyde is observed experimentally only on nasal tissues in rats (both sexes); An equivocal response is observed in mice. - Mechanisms including genotoxicity: regenerative cell proliferation is considered to be the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role at doses inducing regenerative cell proliferation. - Relevance to humans: the epidemiological data illustrates that the local carcinogenic effect observed in rats is relevant to human. The three first elements may in part lower the T25 estimation.	The view of the DS to derive no SCL for locally acting carcinogens following the CLP guidance is supported by rapporteurs.

[3] Dybing E, Sanner T, Roelfzema H, Kroese D, Tennant RW. 1997; T25: a simplified carcinogenic potency index: description of the system and study of correlations. between carcinogenic potency and species/site specificity and mutagenicity. Pharmacol Toxicol. 80(6):272-9.

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		End of attachment no. 3,Section Carcinogenicity		
14/12/ 2011	Belgium/ European Automobile Manufacturers Association	Formaldehyde is a substance with carcinogenic potential for which a non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided the concentrations are below the given limit values. This classification (Germany K4) is supported especially by evidence that, for example, increases in cellular proliferation, inhibition of apoptosis or disturbances in cellular differentiation are important in the mode of action. It takes also into consideration the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationship. Overall the scientific studies lead to different and ambiguous results [4]. Some studies found an association between the exposure to formaldehyde and e.g. leukemia [5] some other studies found no association [6]. The same uncertainties are shown in studies that deal with the relation between exposure to formaldehyde and nasopharyngeal cancer [7].(see Literature list in the pdf file!) ACEA concludes that there is not enough scientific evidence for a clear classification of formaldehyde and refuse the proposed classification as carcinogenic to humans. *ECHA Comment: The attachment: 'ACEA position on Formaldehyde_20111214.pdf' was submitted as a separate attachment. Attachment No. 5*	Noted. Comments are similar to other more detailed comments below; Please see RCOM below. Literature list in the pdf file include study publications that are either discussed in the CLH report or elsewhere in this RCOM (Marsh 2010).	The position is noted.
14/12/ 2011	Belgium/ Formacre	See attached report, p10-p34. Formaldehyde has a very strong epidemiological database (in total about 50000 workers in 3 large cohort studies) and therefore the decision regarding cat. 1A should solely be based on the epidemiology data. Too	This document is similar to the document submitted by APEQ/Lubelia Penedo (attachment 12) and the full comment was pasted in the present table. Please refer to the response to this comment.	Noted, data and references have been considered in the weight of evidence analysis.

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		much weight is placed on a single plant within the National Cancer Institute (NCI) cohort, and even the CLH report states that the grouping of cases in this plant 1 lowers the level of evidence. Because of this limitation, the CLH report relies on further arguments as supportive evidence. Regarding the classification for carcinogenicity cat. 1A we show that - no consistent evidence can be obtained from the NCI cohort. All risk estimates are driven by plant 1 and cannot be generalized as shown by an interaction analysis. - the grouping of cases in plant 1 cannot be explained by the largest number of subjects being exposed to highest peak exposures. The number of workers with highest peak exposure was larger for all other plants, but the NPC incidence was clearly lower. - the correlation of NPC with peak exposure is rather speculative. A sensitivity analysis showed that the low p-value of 0.02 was possibly distorted downward by the small sample size (only 10 NPCs). Further, many NPCs might be related to exposures prior to entering plant 1. And finally the Hauptmann study is incomplete because of 1000 "missing deaths". This can only be clarified by the still missing NCI update. - the case control studies can hardly be used as supportive evidence as demonstrated by a recent metaanalysis. Altogether, the data do not support a causal relationship between formaldehyde exposure and induction of NPC, and do not give sufficient evidence for a cat. 1A classification. The most relevant NCI cohort study is not reliable and its update might lead to a significant reevaluation of the relationship between formaldehyde exposure and NPC. As regards a possible classification for carcinogenicity cat. 1B, the factors listed in section 3.6.2.2.6. (CLP regulation) must be taken into consideration.		

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		FA leads to cytotoxic irritation with increased regenerative cell replication in the nose of exposed rats. Histopathological lesions are already induced after a single day of exposure to the carcinogenic concentrations of 10 and 15 ppm. Extensive ulceration is found after 4 days and squamous metaplasia after 9 days of exposure. Mild effects occur after a few days at 6 ppm. By prolonged exposure such lesions progress to hyperplasia and squamous metaplasia and finally to carcinomas. These data lead to the conclusion that tumor development depends on excessive cytotoxicity leading to increased cell proliferation. Genotoxicity is of minor importance. Without such pronounced cytotoxicity and regenerative cell proliferation no tumors will develop. The toxicological profiles of FA and acetaldehyde are basically identical, apart from their potency, justifying the same classification for FA as that for acetaldehyde, namely cat. 2 under the CLP regulation. In conclusion, three of the criteria given in section 3.6.2.2.6. would lead to a cat. 2 classification decision, namely g. structural similarity to a substance(s) for which there is good evidence for carcinogenicity j. the possibility of a confounding effect of excessive toxicity at test doses k. mode of action and its relevance to humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity. Under these considerations FA was formerly classified as a category 3 carcinogen. Since that time no additional data have been reported that might call the former classification into question and therefore cat. 2 under CLP is still justified. There are positive and negative studies for micronuclei induction in buccal or nasal cells of humans exposed to FA. These data are taken as supportive evidence in the CLH report for the classification of FA as carcinogenic		

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		cat 1A. A weight of evidence assessment showed that the negative studies of Speit et al. (2007a) and Zeller et al. (2011) carried out under strictly defined conditions are most reliable to assess local mutagenicity in the upper respiratory tract of humans. The positive studies on MN induction in workers reported by other authors can by no means be taken as sufficient evidence for such a local mutagenicity. Therefore the overall database on MN induction in nasal or buccal cells in humans cannot be used as supportive evidence for a Cat.1 carcinogenicity classification. *ECHA Comment: The document:' formacare submission.zip' was submitted as a separate attachment. Attachment No.6. which is the same document submitted from Portugal/Lubelia Penedo/APEQ-Protuguese Chemicals Association (attachment no. 12 file name 'Scientific response to French CLH report on formaldehdye.pdf')*		
14/12/ 2011	United States/ American Chemistry Council	Pg. 166-173 As set forth in these comments and in Attachment A, the available human epidemiology data do not support a causal relationship between FA exposure and induction of nasopharyngeal cancer (NPC) and do not correspond to sufficient evidence of carcinogenicity in humans as required for a Carc 1A classification for the reasons listed below: • The extensive reanalyses of the National Cancer Institute (NCI) 2004 data on NPC (Marsh and Youk, 2005; 2007a) that revealed mis-specified and non-robust internal analysis of the NCI data (i.e., NCI's results were driven heavily by anomalous findings for NPC in Plant 1 and NCI neither recognized nor properly accounted for this considerable heterogeneity or interaction structure in the NPC results across the 10 NCI study plants). • The absence of an NPC excess in the large British and NIOSH cohort studies (Coggan et al., 2003; Pinkerton et	- The grouping of most NPC cases in the plant 1 of the NCI cohort is discussed in the CLH report and in the response to specific comments below. - The British and the NIOSH cohorts differ from the NCI cohort by their smaller size (approximately a half of the NCI cohort) as well as in their exposure pattern. The NCI cohort is considered the most important in term of peak exposure. Besides, due to the rarity of NPC the absence or very low number of NPC observed in these studies is considered inconclusive. - It is noted that in Marsh 2007b, several statistical models were tested on relative risks calculations. Although not significant, elevated relative risks	The position is noted and the detailed response of the DS is acknowledged.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		al., 2004). • The absence of a statistically significant association with FA exposure and NPC in an independent study of NCI's Plant 1 (Marsh et al., 2007b). • The finding in a nested case-control study that the NPC excess in Plant 1 of the NCI study may be related to previous employment in the nearby ferrous and non-ferrous metal working industries (Marsh et al., 2007b). • The recent reviews and meta-analyses that confirmed the absence of epidemiological evidence suggesting a causal association for FA exposure and NPC (Chang and Adami, 2006; Bosetti et al., 2007; Duhayon et al., 2008; Bachand et al., 2010). • A detailed evaluation of the impact of missing deaths in the 1994 update (Marsh et al., 2010) that points out the fact that the 1994 NCI risk estimates for NPC are incorrect, as they do not account for the change in person-year counts and possible counts of observed deaths stemming from incomplete follow-up. Because of the current errors in the 1994 NCI cohort data, all evaluations of NPC related to FA exposure, including the CLH Report, must be re-evaluated based on corrected data from the 2004 update of the NCI study. NCI's publication describing the NCI update on morality from solid tumors, including NPC, which would allow for such re-evaluations, is in internal NCI review and pending journal submission. Given the imminent release of the NCI update and the questions raised in the scientific literature, no classification decision should move forward without considering this publication updating the NCI cohort. Therefore, ACC concludes that ECHA should maintain the existing classification, cat 2 or cat. 3 DSD. *ECHA Comment: the document: '2011_ACC submitted comments ECHA FR dossier.pdf' was submitted as a separate attachment. Attachment No.9.*	were found in plant 1 according to different models using continuous peak analysis. Besides, it does not discard the significant excess of risk identified by SMR in Hauptmann 2004 (all plants) and Marsh 2005 (plant 1). - As discussed in the CLH report, the hypothesised cofounder of previous employment in the metal industry cannot explain entirely the highest number of NPC cases in plant 1. The higher number of subjects exposed to formaldehyde peak need also to be considered and the data by Marsh2007b are not considered sufficient to explain the observed increased risk of NPC. - The meta-analysis by Bachand 2010 excluded data from plant 1 of the NCI data. In this study, an overall increase in risk of borderline significance in pooled case-control studies was observed. Besides, Duhayon 2008 and Chang and Adami 2006 did not provide any pooled analysis of formaldehyde data and are not considered as meta-analysis. - As discussed above, the identification of 1000 additional deaths by Beane-Freeman (2009) is not linked to a change in the criteria for inclusion and is not expected to have created a bias of analysis and the results of Hauptmann 2004 are considered valid. Additional specific comments were also provided in the attachment to the pdf file and are discussed below.	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			Regarding specific comment 1 and 2: It is recognised that the result from the NCI cohort is significantly driven by the excess of NPC observed in plant 1. However, plant 1 includes the largest number of subjects in the highest category of exposure to peaks and it may explain why excess of risk is detected in this specific plant. Besides, the hypothesis of a cofounder in plant 1 due to previous work in the metal industry has been raised but was not established convincingly (Marsh 2007a). Finally, the two additional NPC deaths in exposed workers from plants 2-10 both occurred in the highest peak exposure categories so that SMR using local comparisons are also elevated in the highest peak exposure category for plants 2-10 although not significant (Marsh 2005). The NCI cohort therefore overall provides evidence that formaldehyde may induce NPC that is not discarded by the relative grouping of cases in plant 1. Regarding specific comment 3: Exposure to peaks was assessed by an industrial hygienist not only by comparison with the average intensity but also using knowledge of the job tasks. Although it may introduce misclassification, it is not expected to introduce a specific bias in the analysis. Concerning the possible influence of external employment in local metal industries, it is noted that the SMR for NPC in plant 1 calculated based on local	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			NPC rates was higher than when calculated based on national rates. The opposite would be expected in the case of local cofounder such as substantial localisation of metal industry. Finally, as discussed above, the identification of 1000 additional deaths by Beane-Freeman (2009) did not originate is not linked to a change in the criteria for inclusion, it is not expected to have created a bias of analysis and the results of Hauptmann 2004 are considered valid. <u>Regarding specific comment 4:</u> The comment regarding the limitation of case-control studies due to imprecise characterisation of exposure is noted. This criticism is however a general limitation of case-control studies but they however provide epidemiological evidence from a different type of design than cohort studies that is specifically relevant for identification of rare pathologies. Besides, it is less sensitive to specific cofounders that can be present in a cohort population. Several case-control studies report that formaldehyde exposure was associated with an increased risk of NPC and the link with formaldehyde was supported in most studies by a trend with exposure metrics. The results in case-control studies are therefore considered to be relevant in the weight of evidence of formaldehyde carcinogenicity.	
15/12/ 2011	Denmark/ MSCA	Carcinogenicity The classification with Carc 1A H350 is convincingly documented in the CLH proposal.	Noted.	The support is noted

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		There is sufficient human evidence for the proposed classification from the association to the nasopharyngeal cancer from occupational formaldehyde exposure. The plausibility of considering formaldehyde as a site of contact carcinogen is further supported by animal inhalational data showing nasal cancer at low levels of formaldehyde exposure. Cancer at other sites cannot, however, be excluded and a causal association between occupational formaldehyde exposure and leukemia has recently (2009) been concluded by IARC after their reevaluation on formaldehyde. Considering this and as some data indicate a potential for genotoxic effects in tissue distant from the site of contact the classification cannot be linked to the inhalational route alone as carcinogenic effects resulting from exposure from other routes cannot be ruled out.		
15/12/ 2011	The Netherlands/ RIVM	page 159 In the conclusion on carcinogenicity in animal studies, it is concluded that the carcinogenicity of formaldehyde is well established in rats by inhalation with induction of tumours at the site of contact. We agree with this conclusion. However, formaldehyde is negative in mice at concentrations also inducing local cytotoxicity in the nose. It is unclear how this negative result is taken into account on page 171 where it is concluded that there is sufficient evidence because there are two or more independent studies in one species showing the induction of tumours. The reason for the difference in response between rats and mice is unclear. This introduces some uncertainty with regard to extrapolation from the results in rats to humans. Although it is concluded that the mechanism for tumour induction in rat is also relevant, it remains unclear why this mechanism would not apply to mice. Therefore, we have some doubt whether the evidence in animals should be regarded as sufficient evidence or as limited	On animal data, CLP criteria (section 3.6.2.2.3) define sufficient evidence of carcinogenicity in experimental animals when "a causal relationship [...] in (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols"; The repeated and consistent observation of nasal tumours in rats by inhalation in several independent studies therefore constitutes a sufficient level of evidence of carcinogenicity of formaldehyde in experimental animals. It is clear that there is a difference in sensitivity to carcinogenic effect of mice compared to rats: only one study investigated carcinogenicity by inhalation in mice (Kerns 1983) and 2% of males had a nasal squamous cell carcinoma at the	The study in mice can not be interpreted as negative as same precursor lesions and squamous cell carcinomas were seen as in rats. The difference may be that mice are less sensitive than rats as the lowest tumour inducing concentration was 14.3 ppm. More information and a clarification are given in the opinion document

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		evidence. Page 172 There is a significant increase in nasopharynx tumours in both cohort and case-control studies. However, the existence of a grouping in plant 1 of the NCI cohort raises doubts on potential confounders. We do agree that this may be explained by the largest number of subjects exposed to peaks in this specific plant. However, the difference in the number of subjects with peak exposure in plant 1 compared to the other plants is only small and does not fully explain the grouping. We propose to include a table in the CLH report containing the number of subjects with peak exposure and the number of subjects with nasopharynx tumours to get a better overview on this issue. At the moment, the concentration of cases in plant 1 cannot be fully explained. The limited size of the best cohort study and the limited correction for residual confounding by smoking does not add to the confidence in the results. Clearly more independent cohort studies are needed. In conclusion, the epidemiological evidence is limited and confounding cannot be ruled out with sufficient confidence. Therefore, we consider that there is only limited human evidence. Page 176 In our opinion there is only limited human evidence and the evidence in animal studies can also be considered as limited. Therefore, we would propose classification in category 1B based on limited evidence in humans plus limited evidence in animals. We would prefer to use category 1B because this criterion results in a conclusion of presumed human carcinogenicity which is also the wording used for category 1B. The combination of human and animal evidence is strengthened by the fact that the tumours observed in rats and humans both occur at the site of first contact.	highest dose of 14.3 ppm. These tumours are rare in mice and were similar than those observed in rats so that they are likely to be related to formaldehyde exposure and a negative result cannot be concluded. In the same study in rats, squamous cell carcinomas were observed in the nasal cavity at 5.6 ppm (1%) and 14.3 ppm (44%). In rats, formaldehyde inhalation was associated with an exposure-dependent increase in the frequency, severity, and dis- tribution of rhinitis, dysplasia, and squamous metaplasia of the respiratory epithelium lining the anterior nasal cavity. In contrast to rats, mice exhibited marked irritation-induced effects (rhinitis, dysplasia, and squamous metaplasia) only at the highest exposure level. Formaldehyde-induced lesions (squamous metaplasia and inflammation) in mice were much less severe than similar lesions in rats from the same exposure group. The difference in sensitivity between mice and rats is therefore observed for local carcinogenicity and for local cytotoxicity and the difference in sensitivity may be explained by the ability of mice to reduce breathing rate in response to respiratory irritant. Humans are known to be sensitive to the irritant effects of formaldehyde and formaldehyde-induced lesions associated with increased cell proliferation were observed in the nasal passages of	The uncertainties with regard to human data have been considered in the overall conclusion. The proposal has been considered.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Besides the numeration of the tumour response in humans and animals also other factors including those in paragraph 3.6.2.2 have to be taken into consideration when assessing the overall level of concern. In this case especially the possibility of a confounding effect of excessive toxicity at the test doses (j) and the mode of action and its relevance to humans (k) should be considered. The nose tumours in rats occur at dose levels also inducing clear local toxicity. For humans this is unknown. However, it is known that formaldehyde induces local irritation in humans. However, the proposed mechanism includes not only cytotoxicity resulting in growth stimulation but also the mutagenic effect of formaldehyde. Further, the level of irritation in humans is probably limited as several subjects with tumours have been observed. Therefore, these factors are not considered to lower the level of concern for carcinogenicity. Overall, we consider that classification as Carc 1B is warranted based on the criterion that on a case-by-case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.	monkeys exposed to 6 ppm for 1 to 6 weeks (Monticello 1989). The relevance of the rat tumours for humans is therefore considered as high. On the grouping of NPC cases in plant 1 of the NCI cohort, a table summarising the number of subjects with peak exposure and the number of NPC deaths is presented in annex I of this RCOM. The hypothesis of a cofounder in plant 1due to previous employment in metal industry was investigated in Marsh 2007b but failed to explain entirely the cases of NPC in the plant. A non-statistically significant association between NPC and formaldehyde was still observed after adjustment for smoking and metal work job and the association was higher than without adjustment. In this study, analyses by peak exposure groups were not performed. Besides, the evidence provided by the NCI cohort is supported by evidence from case-control studies and by experimental data in rats and biological plausibility in humans. The interpretation of data by RIVM is noted. All together we consider that available data provide a sufficient evidence of carcinogenicity in humans. Most of the additional considerations listed in the CLP criteria relate to the interpretation of experimental data and their discussion is therefore not relevant when effects are identified in	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			humans. Mode of action and its relevance is discussed in the CLH report to assess biological plausibility of NPC tumours in humans and the relevance for humans of the proposed mechanism of action in rodents highly support the epidemiological data.	
15/12/ 2011	United Kingdom/ Momentive Specialty Chemicals UK Limited	Please see detailed comments in attached pdf file <2011_ENVIRON detailed comments on the CLH FR dossier Formaldehyde> (24 pages total). *ECHA Comment: the document: '2011_ENVIRON detailed comments on the CLH FR dossier Formaldehyde.pdf' was submitted as a separate attachment. Attachment No.10. The first 2 pages are copied below:* Dear Committee for Risk Assessment: On behalf of Momentive Specialty Chemicals UK Limited, ENVIRON submits the attached comments on the *Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Substance Name: FORMALDEHYDE.* Our primary comments may be summarized as follows: The above-mentioned report concludes that there is "Significant evidence of an association between formaldehyde exposure and NPC is therefore provided from the most informative cohort study and from several case-control studies and meta-analyses" (pg.167). However, the available epidemiological evidence from cohort and case control studies is	Detailed comments were provided on NPC in the attached document and responses to the main points are given below. On comments on epidemiology, it is underlined that the grouping of cases in plant 1 of the NCI cohort is discussed in the CLH report. Although it raises a doubt on potential cofounder, we do not consider that these results should be excluded from the analysis because: - In the nested case-control study on plant 1 (Marsh 2007a), a previous metal work was not identified for all NPC cases. - Data of previous exposures were scarce and an actual exposure to a suspected risk agent for NPC was not demonstrated. These data are therefore considered insufficient to explain the excess of NPC in plant 1 of the NCI cohort. Besides, a non-statistically significant association between NPC and formaldehyde was still observed after adjustment for smoking and previous metal work. The significant trend identified with exposure to peaks (Hauptmann 2004 and Marsh 2005) further support the	No additional comment, the issue is extensively reflected in the dossier and opinion document.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		inconsistent, and does not generally support a causal connection between formaldehyde exposure and NPC, based on studies in humans. Epidemiological evidence for an association between formaldehyde exposure and NPC is limited to an excess of nasopharyngeal cancers in one plant out of 10 in a large cohort study, and evidence from case-control studies is assessed to be weak. Furthermore, while formaldehyde has been demonstrated to be a nasal carcinogen in rats following exposure to high concentrations with accompanying toxicity, the strength of the evidence suggests a threshold for a carcinogenic effect. The additional information in rats and from the mode of action literature does not provide a basis for elevating formaldehyde from a Category 2 to a Category 1A carcinogen. Elevation to this category relies heavily upon the epidemiological evidence, which is inconsistent as noted above. **Overall, the strength of the epidemiological and toxicological evidence for nasopharyngeal cancers fails to support elevating formaldehyde from a Category 2 to a Category 1A carcinogen.** We respectfully request that the Committee for Risk Assessment consider the primary epidemiological evidence available and the supporting comments to the above conclusions in the attached document. Thank you for your consideration. Yours sincerely	link between exposure to formaldehyde and NPC (all exposed NPC cases in the whole NCI cohort are in the highest category of exposure to peaks). Other cohorts are limited by their smaller size and reduced statistical power to detect an effect. Exposure to peak was also expected to be lower in the NIOSH cohort (described as essentially constant) and is not described in the British cohort. The absence of an excess of risk for NPC in these cohorts does not contradict findings in the NCI cohort. Case-control studies are considered of particular interest to investigate induction of rare tumours such as NPC. Only the studies by West 1993 and Vaughan 2000 indicate a statistically significant association between NPC and formaldehyde. Non statistical association are identified in Marsh 2007a, Vaughan 1986, Roush 1987 and Hildesheim 2001 and supported in these studies by significant trend with exposure to formaldehyde according to at least one metrics. Meta-analyses of Collins 1997 and Bachand 2010 did not find a significant association for case-control studies as the results in both studies were of borderline statistical significance as stated in the CLH report. But Collins 1997 reports a significant association when analysing together cohort and case-control studies (1.3 (1.2-1.5)). In the two latest meta-analyses (Bosetti 2008, Bachand 2010), the results from	

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		Sue Bullock **Principal** *End of page 2 of attachment no. 10*	plant 1 of the NCI cohort were excluded. Although such analyses are interesting to underline the weight of the NCI cohort in the epidemiological weight of evidence, we do not consider that the results from this plant should be excluded for the reason discussed above. For all these reasons, we do not share the conclusion of ENVIRON on epidemiology. On animal data, only one study investigated carcinogenicity by inhalation in mice (Kerns 1983) and 2% of exposed males had a nasal squamous cell carcinoma at the highest dose of 14.3 ppm (it is noted that it represent 2 males out of the 45 animals sacrificed at 24 months – 4%). These tumours are rare and were similar than those observed in rats so that they are likely to be related to formaldehyde exposure and a negative result cannot be concluded. In this study, a difference in sensitivity between mice and rats is also observed for local cytotoxicity and the difference in sensitivity may be explained by the ability of mice to reduce breathing rate in response to respiratory irritant. Carcinogenicity of formaldehyde was tested in one study in hamster and no nasal tumours as well as very limited FA-induced lesions in the respiratory tract were observed. The difference in sensitivity of each species to FA-induced lesions correlates with	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			differences in sensitivity to cytotoxic and regenerative lesions. Known human sensitivity and demonstrated sensitivity of monkeys to such effects highly support the relevance of tumours observed in rats for assessment of FA carcinogenicity in humans. On the mode of action, it is recognised that FA is an endogenous product naturally present in the body. However, it does not exclude that an additional exogenous exposure can induce adverse effects. Endogenous formaldehyde is measured in both rats and humans and the induction of nasal tumours in rats by inhalation shows that exogenous exposure to FA can result in the induction of local tumours and the discussion related to endogenous level is not relevant. Other comments on the mode of action were discussed below in response to comments in the mutagenicity part. Comments were also provided on leukaemia in the attached document but the proposal for classification in 1A mostly relies on NPC and these comments were not reviewed in details.	
15/12/ 2011	Poland/MSCA	Doubts: Carc 1A Comments: Formaldehyde is naturally produced in our body as a part of our normal metabolism and not causes us any harm. The blood level of formaldehyde in non-exposed	The position is noted. These comments are also raised in more details in other comments. Please see response in these RCOM.	Noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		individuals is estimated around 2,61+/-0,14 µg/g (2,05-3,09 µg/g) (Heck et al.., 1982; 1985). Well documented carcinogenic effects were noted only in rats exposed to extremely high concentrations of formaldehyde; Experimental data indicate that formaldehyde has a threshold carcinogenic activity (0.2 mg/m3). The presented in CLH Report proposed classification as Carc 1A is based on nasopharyngeal cancers in humans. However there is a number of doubts such as lack of precise or previous exposure measurement, not taking into account several confounding factors or previous employment. Formaldehyde should be considered as a specific carcinogen with threshold activity. There are serious doubts about practical applications of CLP criteria for classification of evidence of carcinogenicity.		
15/12/ 2011	United Kingdom/ Lonza Switzerland	The CLH Report for Formaldehyde largely based its argument for the reclassification of formaldehyde as a Carc 1A from the epidemiological link of formaldehyde to NPC from a large industrial NCI cohort study. The NAS has indicated that while the NCI study has a number of strengths, they are offset by a number of weaknesses. The excess of NPC cases occurring in one of the 10 plants studied raises significant concerns about the generalizability of the findings to other facilities and other workers exposed to formaldehyde. Also, the NPC findings may have been confounded by previous exposure of these employees to other known carcinogens (i.e., sulphuric acid mists in the presence of inorganic acids). In addition, the nasal cavity tumors in rats are not relevant to humans based on differences in nasal dosimetry. Based on the potential confounding in the cohort study	First, it is noted that the weaknesses of the NCI cohort raised by the National Academy of Sciences (NAS) in their review of the EPA's draft IRIS assessment relate to the use of the NCI cohort for exposure-response and risk assessment. The NAS otherwise concluded that the conclusion of EPA to draw a causal conclusion for NPC and formaldehyde on the basis of the combination of the epidemiologic findings (based on the positive findings of the NCI cohort study and on several case-control studies) with experimental data and mechanistic data was consistent with EPA's guidelines.	

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<tr><th>Date</th><th>Country / Organisation/ MSCA</th><th>Comment</th><th>Dossier submitter's response to comment</th><th>RAC's response to comment</th></tr>
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and the difference in nasal dosimetry in rats versus humans, this is not sufficient evidence to classify formaldehyde as a 1A (CLP) carcinogen. The classification of formaldehyde should be a category 2 (CLP) carcinogen.

ECHA Comment: the document: 'Lonza_Formaldehyde_Comments_111215.doc' was submitted as a separate attachment. Attachment No.11. Page 3-5 is copied below.

<u>EXECUTIVE SUMMARY</u>

Lonza disagrees with the proposed Annex XV classification regarding carcinogenicity because the CLH appears to rely heavily on the Large NCI industrial cohort study (n=25000; Hauptmann et al., 2004) with statistically significant increase (2-fold) in nasopharyngeal cancer (NPC)

1. Large NCI industrial cohort study (n=25000; Hauptmann et al., 2004) with statistically significant increase (2-fold) in nasopharyngeal cancer (NPC)

Weaknesses (National Academy of Science - NAS):

• Excess of NPC cases occurred only in one of the 10 plants studied (plant 1- Wallingford, CT). Seven of the nine NPC deaths occurred in the Wallingford factory.

Table 1 : Number of subjects in each plant
<table>
<tr><th>Plant #</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th><th>7</th><th>8</th></tr>
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</td><td>
Regarding the weaknesses of the NCI cohort, the existence of a grouping of cases in the plant 1 of the NCI cohort has been recognised and discussed in the CLH report. For detailed response to comment on the NCI corhort and results in other cohorts, please see above RCOM to Momentive Specialty Chemicals.

Regarding the differences in FA deposition in the upper respiratory tract between rats and humans, the differences in anatomy and in breathing patterns (exclusive nasal breathing vs oronasal breathing) lead to differences in the local dosimetry. Although carcinogenicity of formaldehyde has not been tested in primates, which are considered as more resembling to humans, Monticello 1989 has demonstrated that inhalation of 6 ppm of formaldehyde for 1 to 6 weeks induces lesions in the nasal passages that were more widespread than in rats. Increases in cell proliferation in monkeys were also detected and were observed in more distal locations of the nasal passages than in rats. The observed local toxicity and carcinogenicity of FA in the respiratory tract of rats is therefore considered highly relevant for primates and humans although differences in localisation may occur.

The difference in response in mice and hamsters is discussed in details above
</td><td>
Proliferation information from primate studies has been added to the opinion document.
</td></tr>
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Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		<table><tr><td>**n**</td><td>426 1</td><td>784</td><td>237 5</td><td>169 2</td><td>744</td><td>524 8</td><td>422 8</td><td>167 9</td></tr></table>	in 1993 RCOM 27 to Momentive Specialty Chemicals.	
		• NPC findings in plant 1 may have been confounded by previous employment of employees in the silver metal industries as Wallingford, CT was a major site for the silver industry as well as the state of Connecticut being a major contributor for the manufacturing of brass. These industries rely heavily on sulfuric acid and inorganic acids and IARC has classified exposure to sulfuric acid mists combined with inorganic acids as a Group 1 carcinogen in humans. Five of the seven NPC cases detected in Plant 1 previously were employed in silver smithing (including brass plating and other jobs related to silver or brass) or other metal work, including steel working and welding. [4] Possible exposure to several risk factors for upper respiratory system cancer (e.g. sulfuric acid mists, mineral acid, metal dust and fumes) may influence the NPC findings unique to Plant 1. Occupational exposure to strong-inorganic-acid mists containing sulfuric acid were linked with cancers of the upper respiratory system.		Strengths and weaknesses of the epidemiology study are taken into account in the weight of evidence consideration.
		• NAS identify the excess of NPC deaths that occurred in Plant 1 as a major weakness in the NCI study. The NAS committee notes the "uncertainties about the causal relationship between formaldehyde exposure and NPC mortality exist" and the lack of NPC findings in the 9 other plants examined need to be considered.[5]		The rat model is considered to be appropriate to identify carcinogenic potential of formaldehyde. Studies in monkeys

[4] Marsh GM et al., 2007. Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers.
[5] Review of the EPA's Draft IRIS Assessment of Formaldehyde. National Research Council of the National Academies, 2011. ISBN: 0-309-21194-8

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		• Published scientific opinions that NCI study design are flawed (incomplete follow-up, unstable risk estimates) (Marsh and Youk, 2005; Marsh et al, 2007) • Large UK industrial cohort study (n=15000; 2003) found only 1 case of NPC in an employee with low formaldehyde exposure. For a general population sample of this size, 2 cases would be expected without any formaldehyde exposure. 2. Induction of tumors in the nasal cavity in rats with a proposed mode of action based on chronic irritation of the respiratory tract and local genotoxicity at doses inducing cytotoxicity and increased proliferation (Regenerative Cell Proliferation- RCP) **Weaknesses:** • Experimental data from the respiratory tract of rats may not be the best model to extrapolate to humans based on differences in nasal dosimetry. The anatomy of rat nasal turbinates is turbulent, which leads to increased deposition of toxicants. In comparison, the human nasal turbinates are not turbulent and therefore have less deposition (Morgan, K,T, A Brief Review of Formaldehyde Carcinogenesis in Relation to Rat Nasal Pathology and Human Health Risk Assessment. Toxicologic Pathology, vol 25, No.3 pp 291-307, 1997). Published literature cites rhesus monkey as a more appropriate model for extrapolation to humans. The inhalation effects of formaldehyde in rhesus monkey have not been studied. • No nasal tumors reported in mice or hamsters		identified differences in susceptibility in regions of the upper respiratory tract that may be related to differences in formaldehyde flux and major deposition sites. Sites of major deposition corresponded well to those sites with microscopic evidence of lesions and increased cell proliferation in rats and monkeys. Of major importance is that the key events are similar across species and therefore the rat data are relevant for humans. The tumour data in mice and hamsters are discussed in the opinion document.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Conclusion **The CLH Report for Formaldehyde largely its argument for the reclassification of formaldehyde as a Carc 1A from the epidemiological link of formaldehyde to NPC from a large industrial NCI cohort study. The NAS has indicated that while the NCI study has a number of strengths, they are offset by a number of weaknesses. The excess of NPC cases occurring in one of the 10 plants studied raises significant concerns about the generalizability of the findings to other facilities and other workers exposed to formaldehyde. Also, the NPC findings may have been confounded by previous exposure of these employees to other known carcinogens (i.e., sulphuric acid mists in the presence of inorganic acids). In addition, the nasal cavity tumors in rats are not relevant to humans based on differences in nasal dosimetry.** **Based on the potential confounding in the cohort study and the difference in nasal dosimetry in rats versus humans, this is not sufficient evidence to classify formaldehyde as a 1A (CLP) carcinogen. The classification of formaldehyde should be a category 2 (CLP) carcinogen.** *End of page3-5 of attachment no. 11*		
15/12/ 2011	Sweden/ MSCA	KemI also agrees with the French Competent Authority that the mode of action for carcinogenicity in the rat nasal cavity is relevant to humans and that the epidemiological evidence on nasopharyngeal carcinomas in humans exposed to formaldehyde is sufficient for the proposed classification as Carc 1A. This conclusion is strengthened by the experimental evidence available on the genotoxicity and carcinogenicity of formaldehyde. KemI notes that The International Agency for Research on Cancer (IARC) has considered that sufficient	The support is noted on NPC.	Noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		epidemiological evidence is available to conclude that formaldehyde also causes myeloid leukemia in humans, while the French Competent Authority has suggested that the available data does not provide causal evidence for formaldehyde to cause myeloid leukemia in humans. We therefore assume that this issue will be further discussed in the Risk assessment committee.		
15/12/ 2011	Portugal/ APEQ- Portuguese Chemicals Association	Please see the Zip file Scientific response to French CLH report formaldehyde.pdf, pgs 10, 14 *ECHA Comment: the document 'FORMALDEHYDE RESPONSE.zip' was submitted as a separate attachment. Attachment No.12. 'Scientific response to French CLH report on formaldehdye.pdf' ,page 10-21 is copied below:* **3. CLASSIFICATION FOR CARCINOGENICITY CAT 1A?** **3.a. Introduction** We agree with the CLH report that any considerations for classification of FA as a human carcinogen (cat. 1A) should predominantly be based on tumors observed in the upper respiratory tract, i.e. nasopharyngeal cancer (NPC). This site corresponds to findings in experimental cancer bioassays as well as to the high reactivity of FA leading to effects only at the site of first contact like DNA protein cross links (DPX), DNA adducts or increased cell proliferation. On the other hand epidemiological data pointing to induction of leukemia are not supported by animal or mechanistic data. As this tumor type is not taken forward to justify cat. 1A, the comments presented here only refer to NPC. We further agree that the study of Hauptmann et al.	**<u>3a</u>** The recent negative meta-analysis on cohort studies by McElvenny 2011 is noted. However, it is published very briefly only as a conference proceedings and it was not included in the revised CLH report. It is also noted that meta-analyses have a limited weight in the assessment of body of evidence that is mainly based on the assessment of each epidemiological study with its strengths and weaknesses. **<u>3c</u>** 1) The grouping of cases in the NCI cohort is discussed in the weight of evidence leading to our classification proposal in cat. 1A. This proposal was highly supported by the positive findings in the NCI cohort <u>and</u> in several case-control studies. Evidence from these two types of epidemiological designs is considered as a proof of consistency. 2) The grouping of cases raise a concern but it is also noted that the	No further comment.

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		(2004) is the most important one for the evaluation of NPC and it was also pivotal for the IARC Cat. 1 decision for NPC. But this is the only cohort study reporting an increased incidence of NPC, while it is not supported by two further large cohort studies (Coggon et al., 2003; Pinkerton et al., 2004). Note that this view is supported by independent reviews (Chang and Adami 2006, Bosetti et al. 2008, Duhayon et al. 2008; Bachand et al. 2010). Note further that a recent re-evaluation of cohort studies by McElvenny and Armstrong (2011) resulted in an overall estimate for the relative risk of NPC of 0.91 (95% CI 0.23 to 1.58) based on 10 studies containing 13 cases. Although this quantitative review included the NCI cohort study the overall risk estimate is below one and unexceptionable. **3.b. CLH summary on epidemiology (NPC)** The CLH report for formaldehyde (Version of 28 September 2011) summarized the scientific justification for the CLH proposal "Carc 1A" as follows (Section 2.2, p. 11): "The biological plausibility of the induction of nasopharyngeal carcinomas in humans exposed to formaldehyde highly supports the consistent epidemiological evidence obtained from the NCI cohort and from several case-control studies. It is considered that the doubt of a potential cofounder is raised by the grouping of cases in the plant 1 of the NCI cohort. But considering the overall database and more specifically the fact that the grouping of cases in plant 1 can also be explained by the largest number of subjects exposed to high peaks in this specific plant, correlation of NPC with the level of peak exposure to formaldehyde, the evidence provided by case-control studies and the biological plausibility, the doubt that the observed induction of NPC may be due to confounder can be ruled	two NPC deaths in exposed workers from plants 2-10 both occurred in the highest peak exposure categories so that SMR using local comparisons are also elevated in the highest peak exposure category for plants 2-10 although not significant (Marsh 2005). 3) The study by Marsh 2007b shows that risk estimates for NPC in the NCI cohort are unstable and that any additional case may impact substantially the results. However, this problem is linked with the rarity of NPC and the difficulty to provide evidence of association for small increases of rare cancers but it does not impact the validity of the results that are actually observed. The study by Marsh 2007a is therefore considered insufficient to explain the excess of NPC in plant 1 of the NCI cohort because: - In the nested case-control study on plant 1 (Marsh 2007a), a previous metal work was not identified for all NPC cases. - Data of previous exposures were scarce and an actual exposure to a suspected risk agent for NPC was not demonstrated. Besides, a non-statistically significant association between NPC and formaldehyde was still observed after adjustment for smoking and previous metal work job and the association was higher than without adjustment. In this	

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		out *with reasonable confidence*. Altogether, the data support a causal relationship between formaldehyde exposure and induction of NPC and corresponds to a sufficient evidence of carcinogenicity in humans." **3.c.Comment on the CLH summary on epidemiology** We do not agree to the following statements cited from the above passage for the reasons given below. 1) *"consistent epidemiological evidence obtained from the NCI cohort".* It is necessary to take into consideration that the evidence obtained from the National Cancer Institute (NCI) cohort, i.e., Hauptmann et al. 2004, is *inconsistent*. Marsh et al. (2007b) showed by an interaction analysis - an important statistical analysis not performed by Hauptmann et al. (2004) - that the risk estimates are modified by plant. Thus, the results of this study are proven to be *inconsistent* and cannot be generalized across plants. 2) *"the grouping of cases in plant 1 can also be explained by the largest number of subjects exposed to high peaks in this specific plant".* Again this statement does not reflect the total database. According to Table 2 in Marsh and Youk (2005) the following description is correct: Plant 1 comprised the highest number of workers with highest peak exposures (n=1964) leading to 6 NPC cases among the exposed. In plants 2-10 the number of workers with highest peak exposures was clearly greater (n=4293) but only 2 NPC cases were observed among the exposed and 2 NPC	study, analyses by peak exposure groups were not performed. Finally, it is noted that the SMR for NPC in plant 1 calculated based on local NPC rates was higher than when calculated based on national rates. The opposite would be expected in the case of local cofounder such as substantial localisation of metal industry. As discussed above in previous comments, the identification of 1000 additional deaths by Beane-Freeman (2009) did not originate from a change in the criteria for inclusion and is not expected to have created a bias of analysis and the results of Hauptmann 2004 are considered valid. 4) As discussed above in previous comments, case-control studies are considered of particular interest to investigate induction of rare tumours such as NPC. Only the studies by West 1993 and Vaughan 2000 indicate a statistically significant association between NPC and formaldehyde, non statistical association are identified in Marsh 2007a, Vaughan 1986, Roush 1987 and Hildesheim 2001 and supported in these studies by significant trend with exposure to formaldehyde according to at least one metrics.	

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		cases were observed in the unexposed as defined by Hauptmann. Note further, that the NPC risk at Plant 1 is significantly different from all other plants even after taking cumulative and peak exposures into account, i.e., the elevated NPC risk cannot be explained by higher exposures in Plant 1 (Marsh et al. 2007b). 3) *"can also be explained by the … correlation of NPC with the level of peak exposure to formaldehyde"* There are several reasons why this statement cannot be taken as proven but rather is speculative. First, as the evidence for the association between NPC and Formaldehyde is only based on 10 cases in the Hauptmann study, Marsh et al. (2007b) carried out a sensitivity analysis to look for indications of a small sample bias that often tends to exaggerate risk estimates and to produce artificially low p-values. They performed a systematic sensitivity analysis by adding repeatedly one additional NPC case to all of the 117 different exposure situations. Only 42% of the scenarios returned a p-value < 0.05. Thus, the p-value of 0.02 belonging to the Hauptmann analysis was not representative and possibly was distorted downward by a small sample bias. This analysis showed that the "correlation" was much more unstable than the p-value reported by Hauptmann et al. leads one to believe. Second, an explorative study by Marsh et al (2007a) indicated that 5 out of 7 NPC cases from plant 1 (only 6 cases according to Hauptmann et al. 2004) might be associated with exposure to potential confounders through previous employment in silver smithing or other metal work before they were hired at the plant. This also sheds doubt on the "correlation". Third, the Hauptmann et al. (2004) study is incomplete.	**<u>4a</u>** These factors need to be discussed when the decision is essentially based on experimental data and it is therefore not relevant to the formaldehyde proposed classification in category 1A. The following RCOM can however be made: f) The difference in sensitivity of each species to FA-induced tumours correlates with differences in sensitivity to cytotoxic and regenerative lesions as discussed in previous RCOM. Known human sensitivity and demonstrated sensitivity of monkeys to such effects highly support the relevance of tumours observed in rats for assessment of FA carcinogenicity in humans. g) Based on experimental and epidemiological data the criteria for classification of FA as a carcinogen 1A are fulfilled. Parallel assessment of other aldehydes shows similarities and differences that would need to be discussed in details before to consider potential read-across. Such discussions are out of the scope of the current proposal for classification that focus on formaldehyde but it is noted that as FA is the best investigated aldehyde, a	Factors and Formaldehyde-related data have

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		The authors failed to perform a sufficiently complete follow-up in mortality. They documented 8486 deaths but missed approximately 1000 deceased. These "missing deaths" were not evenly distributed, but the percent increase in revised deaths among "unexposed" workers was twice that of the "exposed" for all deaths, all cancer deaths, and all solid neoplasms. If these missing deaths are taken into account, there is a decrease in the relative risks in comparison to the original calculations, e.g. for all lymphohematopoetic malignancies or leukemia. NCI, however, did not report on the effect of these missing deaths on NPCs. Although Marsh et al. (2010) highlighted the problem of these missing deaths for the analysis of NPC no further information has been published in this regard by NCI. 4) *"can also be explained by … the evidence provided by case-control studies* " The case control studies have to be assessed in a more detailed manner. Bachand et al. (2010) performed a meta-analysis and found significantly increased odds ratios in case-control studies, but the summary odds ratio for smoking adjusted studies was no longer significantly increased with an unexceptionable estimate of 1.10 (95% CI: 0.80, 1.50). Thus, the above statement about case-control studies is invalid when smoking habits are taken into account. In addition it has to be taken into account that the database of the most relevant cohort study is not reliable and that the soon to be expected NCI cohort study update might lead to a relevant reevaluation of the relationship between formaldehyde exposure and NPC**.** **Altogether, the data <u>do not support</u> a causal relationship between formaldehyde exposure and**	relevant read-across would be to apply the FA classification to less investigated aldehydes with sufficiently similar toxicological profile. i) The result of the new study investigating FA in blood after inhalation is noted (Kleinnijenhuis 2011) but access to this draft TNO report was not available and it is therefore not included in the CLH report. Results of this new study seems however to support previous results. On deposition sites and DPX, we are not aware of studies investigating DPX in the bone marrow in monkeys (Moeller 2011 investigates adducts but not DPX) and in olfactory mucosa and bone marrow in rats. k) As discussed in the mutagenicity part we consider that there is sufficient evidence showing local mutagenicity of formaldehyde *in vivo*.	been considered in the weight of evidence analysis.

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		induction of NPC and <u>do not correspond</u> to a sufficient evidence of carcinogenicity in humans as required for a cat. 1A classification. **4. CLASSIFICATION FOR CARCINOGENICITY CAT. 1B?** **4.a. Regulatory situation** Section 3.6. of Regulation (EC) No 1292/2008 (16 December 2008) relates to carcinogenicity. According to section 3.6.2.2.5. there are several factors that "can be viewed as either increasing or decreasing the level of concern for human carcinogenicity." These are listed in section 3.6.2.2.6. as follows: a. "tumor type and background incidence b. multi-site responses c. progression of lesions to malignancy d. reduced tumor latency e. whether responses are in single or both sexes f. whether responses are in a single species or several species g. structural similarity to a substance(s) for which there is good evidence for carcinogenicity h. routes of exposure i. comparison of absorption, distribution, metabolism and excretion between test animals and humans j. the possibility of a confounding effect of excessive toxicity at test doses k. mode of action and its relevance to humans, such as *cytotoxicity with growth stimulation (emphasis added)*, mitogenesis, immunosuppression, mutagenicity."		

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		4.b. Assessment of the criteria a-k given in section 3.6.2.2.6 a) tumor type and background incidence Inhalation of FA at high concentrations leads to the induction of nasal tumors starting around 6 ppm (Kerns et al., 1983; Monticello et al., 1996). The dose response curve is highly non-linear. The tumors originate from the respiratory epithelium in the anterior part of the nose (Morgan et al., 1986a). The spontaneous incidence of squamous cell carcinomas in the nose is very low (Conolly et al., 2003). b) multi-site responses FA inhalation has only resulted in nasal tumors in experimental animals. c) progression of lesions to malignancy Already after 1 day of exposure to the clearly carcinogenic concentrations of 10 and 15 ppm epithelial cell degeneration, single cell necrosis and epithelial exfoliation were observed. These lesions progressed to local ulceration, epithelial hyperplasia and squamous metaplasia after 4-9 days of exposure. Lesions at 6 ppm were only mild single cell necrosis and patchy hyperplasia (Swenberg et al., 1983a; Morgan et al., 1986b, Monticello et al., 1991). Exposure over 6 weeks and longer led to clear epithelial hyperplasia and squamous metaplasia at 10 and 15 ppm and mild effects at 6 ppm. No lesions were found at 2 ppm and below (Monticello et al., 1996). Thus, at carcinogenic exposure concentrations lesions progressed with exposure duration from single cell necrosis and local ulceration via epithelial hyperplasia and squamous metaplasia finally to squamous cell carcinomas. d) reduced tumor latency		

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		Exposure to high FA concentration led to a clear reduction of tumor latency. First tumors already became apparent within the first year of exposure to 15 ppm (Swenberg et al., 1980; Albert at al., 1982; Sellakumar et al., 1985). e) whether responses are in single or both sexes The carcinogenic response in the nose of rats is independent of the sex (Kerns et al., 1983). f) whether responses are in a single species or several species Mice (Kerns et al., 1983) and hamsters (Dalbey, 1982) are by far less susceptible to nasal tumor induction after inhalation exposure to FA than rats. There is no indication for such an effect in hamsters, but in mice at very high concentrations these tumors may occur as evidenced by 2 nasal tumors at 15 ppm. g) structural similarity to a substance(s) for which there is good evidence for carcinogenicity As FA is by far the best investigated chemical within the group of aldehydes, data derived from other aldehydes do not add much further evidence to evaluate the carcinogenic potential of FA. Aldehydes with a carcinogenic or mutagenic effect have been evaluated by the German MAK Commission and the evaluations for acetaldehyde (MAK, 2008), acrolein (MAK, 1997) and glutaraldehyde (MAK, 2002, 2006) are briefly summarized here. All these substances have been tested for carcinogenicity, either by oral or inhalation exposure. They all exhibit a genotoxic potential in different test system.		

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		Acetaldehyde (MAK, 2008): similar to FA, acetaldehyde is an endogenous metabolite and endogenous DNA adducts have been found. After inhalation exposure the olfactory epithelium is more susceptible to acetaldehyde than the respiratory epithelium. Already 5 weeks of exposure to 243 ppm lead to degeneration of the olfactory and 3 days at 750 ppm to single cell necrosis. After 26 weeks at 1500 ppm hyper- and metaplasia of the respiratory epithelium are observed. Long term exposure leads to a high incidence of adenocarcinoma of the olfactory epithelium at 750 ppm, while squamous cell carcinoma of the respiratory epithelium only occurred at 1500 ppm. It is assumed that similar to FA local tissue damage is a prerequisite for tumor induction. But due to the lack of detailed dose response data a final decision is not possible whether the carcinogenic response is primarily caused by a genotoxic or a cytotoxic mechanism. Acrolein (MAK, 1997): this substance with a double bond in conjugation to the carbonyl group is highly reactive to nucleophilic substances. This explains its severe local irritation and genotoxicity (among others leading to DNA adducts in vivo) similar to FA. In vivo mutagenic or cytogenetic effects have not been found. Increased cell proliferation and slight histopathological changes in the nasal epithelium of rats were already observed after inhalation exposure for 3 days at 0.25 ppm. In a 90 day study rats developed histopathological alterations (e.g. hyper- and metaplasia) in nasal tissue at 0.4 ppm and a NOAEL could not be established. In comparison with FA, the histopathological lesions at 0.67 ppm after 3 days of inhalation exposure corresponded approximately to those observed with FA at 3.2 ppm. A further comparison with FA is not possible since a carcinogenicity study by inhalation is not available for acrolein. The results of an oral carcinogenicity study are given in the section on		

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		exposure routes. Glutaraldehyde (MAK, 2002, 2006): for genotoxicity/mutagenicity positive and negative results have been reported in in vitro systems, while in vivo after oral and inhalation exposure mutagenic effects were not found. In a 13 week study with exposure levels between 0.0625 and 1 ppm increased cell proliferation of the squamous cell epithelium in the nasal vestibulum occurred in rats at 0.25 ppm and in mice already at 0.0625 ppm. Persistent metaplasia of the respiratory epithelium was found in both species starting at 0.5 ppm. Thus, in contrast to FA leading predominantly to effects in the respiratory epithelium, for glutaraldehyde the vestibulum is the most sensitive part of the nose. A 2-year carcinogenicity study has been carried out with rats (0.25, 0.5, 0.75 ppm) and mice (0.0625, 0.125, 0.25 ppm). In rats hyperplasia and inflammation of the squamous epithelium started at 0.25 ppm in the nasal vestibulum and at 0.5 ppm in the respiratory epithelium. In mice already at 0.0125 ppm metaplasia of the squamous epithelium was observed. In comparison to FA inflammation predominated in the anterior parts of the nose. Neither local nor systemic tumors were observed. A dosimetric comparison for the induction of hyperplasia and squamous cell metaplasia showed that 0.5 and 0.75 ppm glutaraldehyde would correspond to about 6 and 10 ppm FA. But at these comparable concentrations glutaraldehyde did not lead to preneoplastic changes in contrast to FA. The lack of a local carcinogenic activity may either be explained by the relationship of genotoxicity vs cytotoxicity or by the predominant action on the anterior nose covered by the more resistant squamous epithelium. The results of oral carcinogenicity studies are given in the section on exposure routes. With the framework of EU regulations acetaldehyde has		

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		been classified as carcinogenic cat. 3 (under the old DSD regulation), but not acrolein and glutaraldehyde due to lack of positive carcinogenicity data. As classification is hazard based, the similarities in the toxicological profile between GA and acetaldehyde, apart from potency, justify FA to be treated like acetaldehyde. In summary, there are some other aldehydes that can be assessed in parallel to FA, namely acetaldehyde, acrolein and glutaraldehyde. All of these aldehydes are genotoxic and for acetaldehyde, similar to FA, endogenous DNA adducts have been found. Acetaldehyde is carcinogenic after inhalation but due to its lower reactivity at much higher concentrations. The biological reactivity of acrolein (with a double bond in conjugation to the aldehyde function) and glutaraldehyde (with two carbonyl groups) is much higher than that of FA. For acrolein no carcinogenicity study by inhalation is available, and glutaraldehyde did not lead to tumors at clearly cytotoxic concentrations. This may either be explained by the relationship of genotoxicity vs cytotoxicity or by the predominant action on the anterior nose covered by the more resistant squamous epithelium. The similar toxicological profiles of acetaldehyde and FA justify the same classification of FA as for acetaldehyde, i.e. cat 3 (old DSD system). h) routes of exposure A clear carcinogenic response was only observed in rats after inhalation exposure. Findings after oral and dermal exposure will be discussed in more detail in the section on exposure route. i) comparison of absorption, distribution, metabolism and excretion between test animals and humans		

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		Metabolism: Glutathione-dependent cytosolic FA dehydrogenase (FDH) is the most efficient detoxifying enzyme system (Uotila and Koivusalo, 1989). FDH is highly conserved in all species (Jörnvall et al., 2000). It was found in all tissues investigated (Julia et al., 1987; Uotila and Koivusalo, 1996; Haselbeck and Duester, 1997), including the respiratory tract and nasal respiratory and olfactory mucosa (Keller et al., 1990; Casanova-Schmitz et al., 1984a; Maier et al., 1999). Metabolic detoxification leads to a rapid metabolism of FA with a biological half life of 1-1.5 min (Rietbrock, 1965, 1969; Malorny et al., 1965; McMartin et al., 1979). The detoxification pathway via formaldehyde dehydrogenase is half saturated in rats at exposure concentrations of 2.6 ppm (Casanova et al., 1989). *Endogenous vs. exogenous FA:* The total endogenous FA production in humans has been calculated to be 2450 mg/h (Cascieri and Clary, 1992) and the amount detoxified in the liver as 1320 mg/h (Owen et al., 1990). Endogenous FA concentrations (free and reversibly bound) in blood and tissues of humans and animals are in the range of a few µg/g wet tissue weight (Heck et al., 1982, 1985; Casanova et al., 1988). Inhalation of 6 or 14.4 ppm (rats) (Heck et al., 1982, 1985), 6 ppm (monkeys) (Casanova et al., 1988), or 1.9 ppm (humans) (Heck et al., 1985) did not lead to an increase of the FA concentrations in blood. In some of these studies the time span between end of exposure and analysis might have been too long allowing for metabolic degradation of exogenous FA by taking into account the short biological half life of FA. Therefore a new study was carried out. Rats were exposed to 10 ppm 13C-FA over 6 h. Blood was withdrawn during exposure (at 3 h), directly after exposure and at some time points thereafter. The sensitivity of the method allowed to determine exogenous labelled FA in the blood		

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		at a concentration of about 1.5% of that of endogenous FA. No increase of FA stemming from the exogenous labelled substance could be detected in the blood at any time point (Kleinnijenhuis, Staal, 2011). A mathematical model for the absorption and metabolism of FA vapor showed that FA is rapidly removed by the nasal tissue and the increase of FA in blood was insignificant compared to preexisting blood concentrations (Franks, 2005). *Species differences:* FA is a nasal irritant leading to reflectoric depression of respiratory rate and minute volume in rats and mice. This response is much more pronounced in mice as compared to rats (Chang et al., 1981, 1983; Jaeger and Gearhart, 1982) leading to a markedly reduced delivered dose at the nasal surface in mice in comparison to rats. The difference in delivered dose is a good semi-quantitative explanation for the different responses of rats and mice to nasal tumor induction (Barrow et al., 1980, 1986). *Deposition sites identified by cell proliferation and DNA-protein cross links (DPX):* Histopathological lesions and cell proliferation rates in the nasal passages of rats correspond well to the sites of tumor development after exposure to FA (Monticello et al., 1991, 1996; Casanova et al., 1994). In the monkey at 6 ppm the lesions and increased cell proliferation are not confined to the nose but extend to the larynx, trachea and carina but in much smaller quantities (Monticello et al., 1989; Heck et al., 1989). No effects were found in the maxillary sinus of monkeys (Heck et al., 1989; Casanova et al., 1994) and for DPX formation in the proximal lung and bone marrow. In rats DPX formation only occurs in the nasal respiratory mucosa with a good correlation to the sites for tumor development, but not in the olfactory mucosa or bone marrow.		

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		j) the possibility of a confounding effect of excessive toxicity at test doses Alterations of the nasal epithelium already occur after a single exposure to the carcinogenic concentration of 10 and 15 ppm with progression to extensive ulceration after 4 days and hyperplasia and squamous metaplasia after 9 days of exposure. Early squamous metaplasia was already detected after 4-5 days at 15 ppm. Much less severe lesions are induced by 6 ppm with only minimal focal hyperplasia and squamous metaplasia starting after exposure durations of 9 days (Swenberg et al., 1983a; Morgan et al., 1986b; Monticello et al., 1991). No histopathological abnormalities were observed at 0.7 and 2 ppm for exposures up to 18 months and only mild alterations at 6 ppm (Swenberg et al., 1986). Severe histopathological lesions were noted in the nose of rats after prolonged exposure to the carcinogenic concentrations of 10 and 15 ppm (Monticello et al., 1996; Casanova et al., 1994). Initial increases of cell proliferation that were noted in an early investigation after exposure to 0.5 and 2 ppm returned to control rate after 3-9 days; increased cell proliferation at 6 ppm observed after 6 weeks returned to base line after 3 months (Monticello et al., 1991, 1996). Thus, excessive toxicity already after a few days of exposure at carcinogenic exposure concentrations leading to an increase in cell proliferation has been described in many experiments and is obviously a prerequisite for tumor development. At low exposure concentrations up to 6 ppm initially increased cell proliferation decreased and eventually returned to control levels with prolonged exposure. The guidance for classification according to CLP defines		

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		this criterion j among others as follows (p. 204): "Excessive toxicity, for instance toxicity at doses exceeding the MTD, can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which can lead to tumor development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumors at lower less toxic doses." And also the CLH report states in this respect (p.11): "Data investigating the mode of action support the existence of a threshold type mode of action for its carcinogenic properties based on the cytotoxic effect of formaldehyde. Genotoxicity is also expected to play a role above this threshold." Thus the criterion j has to be taken into consideration for the carcinogenicity classification of FA. k) mode of action and its relevance to humans, such as *cytotoxicity with growth stimulation*, mitogenesis, immunosuppression, mutagenicity The underlying mode of action for the carcinogenic effect of FA in rats after inhalation is regenerative cell proliferation caused by cytotoxicity. Various genotoxic and mutagenic effects of FA have been described in vitro, but there is no reliable evidence for mutagenicity in vivo (see section on mutagenicity). Therefore, genotoxicity is considered to be of minor importance for tumor development. No mutations were detected in the p53 and K-ras genes in rats after inhalation exposure (Meng et al., 2010). Tumor development, cytotoxicity, cell proliferation and formation of DNA-adducts and DPX all show a highly non-linear dose response relationship that has also been demonstrated for gene expression (Andersen et al., 2008). Without cytotoxic irritation tumor development in the respiratory tract is not to be expected (MAK, 2000; McGregor et al., 2006).		

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		The guidance for classification according to CLP defines this criterion k among others as follows (p. 205): "the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation) may lead to a downgrading of a Category 1 to Category 2 classification." Again this criterion is fulfilled for the local action of FA. For systemic tumors caused by FA exposure there is no convincing evidence from animal experiments. Furthermore, mechanistic studies have not given any plausible mechanism how such tumors at distant sites from the port of entry might develop (Heck and Casanova, 2004). Mechanisms recently proposed for leukemia induction (Zhang et al., 2009, 2010) are far from conclusive. In contrast, there is strong mechanistic evidence that a genotoxic activity of FA in the form of DNA adducts is only restricted to the site of first contact (Lu et al., 2010, 2011, 2011a; Moeller et al., 2011). *End of attachment no. 12 page 10-21 Carcinogenicity.*		
20/12/ 2011	France/ Women in Europe for a Common Future	*ECHA Comment: Due to technical problem after ECHA launched new web site on 15 December 2011, the'Give Comments' link was active and this comment was received.* *Attachment no. 14 'WECF formaldehyde consultation.pdf' has the same content.* conclusions page 10: Formaldehyde is classified by International Agency on Research on Cancer as carcinogenic to humans (Group 1): In addition to sufficient evidence in experimental animals for upper airway carcinogenicity, IARC concluded that there is sufficient epidemiological evidence that formaldehyde	The information is noted and is in line with our assessment.	Noted.

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		causes nasopharyngeal cancer in humans.		

Mutagenicity

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
28/11/2011	United Kingdom / Individual	Why does the UK Government allow the use of artificial sweeteners in products in this country which are known to be linked to mutagenic reactions in humans? Surely this is not in the interest of good public health and can only benefit the chemical companies that manufacture the substance.	Noted (not in the scope of the discussion).	No comment.
06/12/2011	Germany/ Individual	see attached document *ECHA comment: Attached document "Comments on the CLH Report for Formaldehyde" (FA_CLH.pdf) is attached separately. Attachment No. 1. Part of the attachment is copied below.* My name is Günter Speit, I am professor of Human Genetics at the Ulm University (Germany). My research activities are focussed on Environmental Mutagenesis and the mechanisms of mutagenesis and DNA repair. Since several years I am doing research on formaldehyde genotoxicity / mutagenicity. These research activities were initially supported by the Department of Environment of the State of Baden-Württemberg (Germany) and are now financially supported by the European Chemical Industry Council (CEFIC). Despite this industrial financial support, I am an independent scientist and the results of my research are published in internationally recognized peer reviewed journals. My concern has always been protection of health at the workplace and consumer protection. I served on national and international scientific committees (MAK commission, SCCP) and was responsible for the evaluation of genotoxicity / mutagenicity data. I am at present the president of the European Environmental Mutagen Society (EEMS). As a member of the "ad hoc Working Group Formaldehyde" at the German Federal Institute of Risk Assessment (BfR), I am directly involved in discussions about classification and regulation of formaldehyde. My C.V. is attached for further information. I am concerned about the evaluation of the genotoxicity / mutagenicity data in the CLH report and their interpretation with regard to relevance for	**Experimental data *in vitro*:** we agree that *in vitro* data points toward a clastogenic mode of action. However, it is noted that positive results in gene mutation assay on mammalian cells were also observed in Grafström 1990 and 1993, Blackburn 1991, Mackerer 1996, Liber 1989. In most of these studies, the type of mutations was not investigated. In Liber 1989, 30	**Experimental data *in vitro*:** We agree with the conclusion that formaldehyde should be regarded as an in vitro mutagen with a predominantly clastogenic mode of action. The results of gene mutation tests (HPRT test in V79: Grafström, 1990; Merck, 1989) are contradictory: The positive result in an MLA (Speit, 2002) based on an increase in the frequency of small

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		carcinogenesis. Therfore, I would like to make some comments - in particular with regard to the *in vivo* data and the human data. **Experimental data; *in vitro*** Formaldehyde (FA) is genotoxic and mutagenic in vitro. Of particular interest are the results obtained with mammalian (including human) cells. FA clearly induces chromosomal effects (chromosome aberrations, micronuclei and sister chromatid exchanges) but is a weak inducer of "true" gene mutations. FA is negative in the *in vitro* HPRT gene mutation assay under standard test conditions (Merk and Speit, 1998) and positive effects in the mouse lymphoma TK gene mutation assay are mainly due to small chromosomal effects (Speit and Merk, 2002). Consequently, besides the conclusion that FA "has the potential to damage DNA *in vitro*", FA should be regarded as an *in vitro* mutagen with a predominant clastogenic mode of action. This means that chromosomal effects are sensitive indicators of FA-induced genotoxicity / mutagenicity and are of special interest for the evaluation of the *in vivo* mutagenicity of FA. **Experimental data; *in vivo* at the site of contact** Inhalation of FA induced DPX in experimental animals in the nose and the upper respiratory tract. However, there is no convincing experimental evidence that mutations are induced in proliferating cells which is a prerequisite for the induction of cancer. DPX can be induced and are measured in all cell types (proliferating and non-proliferating) and in all layers of the mucosa. The formation of mutations (e.g., chromosomal mutations: micronuclei, MN) in nasal epithelium requires that basal layer cells are sufficiently exposed, that the chromosomal DNA of these cells is damaged and that incompletely repaired DNA lesions (e.g., DPX) lead to the formation of MN during replication. We demonstrated by *in vitro* co-cultivation experiments that FA that has entered nasal epithelial cells is not released and does not damage other cells in close proximity to the epithelial cells (Neuss et al., 2010a). This means that under *in vivo* conditions with environmental or occupational exposure to FA, it is highly unlikely that there is sufficient direct exposure of basal cells which may induce mutations. Our in vitro studies are in accordance with an *in vivo* micronucleus tests (MNT) performed in nasal epithelial cells of rats after exposure to FA by inhalation for four weeks with FA concentrations	mutants were analysed and half of them had point mutations while others showed complete or partial deletion of the HPRT gene. The capacity of FA to also induce 'true' gene mutations may not entirely be dismissed although we agree that clastogenic effects are sensitive indicators of FA genotoxicity. **Experimental data *in vivo* at the site of contact**: the fact that formaldehyde is not expected to be released from epithelial cells does not show that basal cells may not be exposed to formaldehyde. The observation of DPX in all layers of the mucosa supports	colonies, suggestive of chromosomal aberrations. Only marginal increase in the frequency of large colonies, suggestive of gene mutations was observed. **Experimental data *in vivo* at the site of contact**: We agree with the conclusion that there is clear evidence for induction of genotoxic effects (DPX) by formaldehyde at site of contact (nasal mucosa) in rats. We agree with the conclusion that there is no clear evidence for the induction of mutations at site of contact in consequence of both inhalation and oral administration of formaldehyde. The tests should be

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		up to 15 ppm (Speit et al., 2011). Under these experimental conditions, no increased MN frequencies were measured in nasal epithelial cells. We pointed out that these results have to be interpreted with care because MNT with rat nasal epithelial cells is not an established test system and a positive control to demonstrate the sensitivity of the test was not available. However, the study design and the extent of the evaluation (10,000 - 12,000 cells per dose group) should be suited to detect an effect if MN were actually induced. We have also shown in our inhalation study with rats that FA did not induce DPX (indirectly measured by the comet assay) and MN in broncho-alveolar lavage (BAL) cells (Neuss et al., 2010b). Only one published study (Dallas et al., 1992) reported increased frequencies of chromosome aberrations in lung lavage cells of rats after repeated exposure to 15 ppm FA for one or eight weeks. This positive result suggests that under the (high) exposure conditions of this study, inhalation of FA might cause a genetically relevant exposure of the lung. However, in my opinion, this study is not fully reliable because it is known that the preparation of chromosomes from macrophages is problematic with regard to the available number of metaphases and the quality of the chromosomes. This may explain why only 50 cells per animal were investigated. Furthermore the high background frequency of chromosome aberrations (3.5 and 4.4%) is a matter of concern and may be due a poor quality of the chromosome preparation. The MNT used in our study is surely more sensitive and reliable and revealed a clear negative result after analysis of 2,000 cells per animal and 12,000 cells per group. Our results were confirmed by a clear negative result obtained with the comet assay for the detection of DNA strand breaks and DPX in BAL cells under these experimental conditions. It has also been shown that FA inhalation up to 15 ppm for 13 weeks did not induce gene mutations in tumor-related genes (p53, K-ras) in the nasal mucosa of rats (Meng et al., 2010). The increased frequency of mutations in the p53 gene measured in tumors of rats after exposure to 1 5 ppm (Recio et al., 1992) are most likely not directly induced by FA but occurred as secondary events (with a selective advantage) in the process of carcinogenesis. In summary, there is clear evidence for the induction of genotoxic effects (DPX) by FA at the site of contact. This has also be confirmed by the detection of other kinds of DNA lesion in nasal cells from rats exposed to FA by highly sensitive analytical methods (Lu et al., 2010; Moeller et al., 2011). However there is no sufficient proof for the induction of mutations in nasal epithelium	the possibility of a direct contact of proliferating cells in the mucosa with formaldehyde. The recent study Speit 2011 did not detect micronuclei in the nasal epithelium of rats exposed through a wide range of FA concentrations and up to 15 ppm for 4 weeks. The limitations of this study include: 1/ an absence of positive response in the positive control but it is noted that no validated positive control is available for investigation of nasal epithelium by the inhalation route. It is not known whether the control that was used (cyclophosphamide by gavage) lead to a sufficient exposure of the targeted tissue and the absence of	interpreted with care because they usually included limitations. *1. inhalative exposure:* Dallas et al. (1992) reported on a marginal but statistically significant increase in chromosomal aberrations in the pulmonary lavage cells from rats after inhalation of FA (limitations: high background frequency of chromosomal aberrations; no positive control). An induction of chromosomal aberration in broncho-alveolar lavage cells of rats was not confirmed by Neuss et al. (2010c) in a micronucleus test (limitation: positive control did not give an appropriate response for micronuclei induction). However, Sul et al. (2007) observed an

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		cells after inhalation of FA. Mutations may occur under extreme conditions when all cellular defence mechanisms (unspecific binding, metabolic inactivation, repair of induced DNA damage) are overwhelmed. At present, it remains unclear whether or to what extent mutagenicity contributes to FA-induced carcinogenicity in the nasal mucosa of rats. **Experimental data; *in vivo* on somatic cells at distant sites of exposure** There is overwhelming evidence that FA does not induce genotoxic and mutagenic effects at distant sites of exposure. We have clearly shown that FA does not induce DPX, SCE and MN in peripheral blood of rats exposed by inhalation (Speit et al., 2009). This study used standard *in vivo* genotoxicity tests for the evaluation of potential mutagens for regulatory purposes in accordance with international guidelines and recommendations for mutagenicity testing. These clear negative results have a high degree of reliability and are consistent with other well-performed in vivo genotoxicity tests (e.g. Kligerman et al., 1984) and all what is known about the toxicokinetics of FA (IARC, 2006). In my opinion, it is inappropriate to seriously consider the studies by Kitaeva and co-workers and the group of Sul and lm. These studies have been criticized in detail (BfR, 2006; Speit, 2006) and it is clear that they lack reliability and plausibility. On the contrary, excellent experimental studies have been published by the Swenberg group (Lu et a\.,2010; Moeller et al., 2011) which clearly demonstrate that FA exclusively acts as a genotoxin at the site of first contact and distant site effects do not occur after inhalation of FA. In summary, FA is a kind of textbook example for a locally acting (geno-) toxin and genetically relevant effects at distant sites of exposure are highly unlikely. **Experimental data; *in vivo* on germ cells** Genotoxic and mutagenic effects on germ cells require sufficient exposure of the germ cells (or gonads). Considering the overwhelming evidence that FA is not systemically available, a relevant potential for reaching the gonads and inducing germ cell mutations can be excluded. There is no convincing experimental evidence for germ cell mutagenesis after FA inhalation. There is no basis for a classification of FA as a germ cell mutagen. **Human data; in humans at the site of contact** There are several studies which report an increase in the frequency of MN in	response may not show an absence of sensitivity of the assay. 2/ a high experimental variability in the background micronuclei frequency possibly limiting the identification of statistically significant effects. 3/ It has been shown that the whole nasal mucosa in rats does not exhibit a similar sensitivity to inhaled FA due to tissue sensitivity and regional dosimetry. Analysis of the whole nasal epithelium may dilute the capacity to detect an effect restricted to the most sensitive part of the epithelium. The number of cells scored in this assay was consistent with the requirements of	increased DNA damage in lung cells from rats after inhalation of FA (limitation: without taking into account a positive control). A recent study by Speit et al. (2011) showed no increased micronuclei frequencies in nasal epithel cells of rats (limitations: no established test system; no positive control). *2. oral administration:* Migliore et al. (1989) reported on the induction of micronuclei in cells of the gastro-intestinal epithelium of rats treated orally with FA (limitations: effect only in conjunction with signs of severe local irritations; questionable relevance of the positive control). **Experimental data *in vivo* on somatic**

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		buccal or nasal cells of subjects exposed to FA. We did not find such an effect in volunteers exposed to FA by inhalation under strictly controlled conditions (Speit et al., 2007; Zeller et al., 2011). It is nearly impossible to find potential explanations for the conflicting results. There are differences in the period of exposure, the average exposure levels and the peak exposures. A comparative evaluation of the positive studies does not give a consistent picture (Speit and Schmid, 2006). The main problem is the lack of standardization of the MNT with exfoliated cells. This is reflected by the use of a variety of cell sampling- , preparation- and staining procedures, leading to large variations in the background frequencies of MN in control populations. The time kinetics of MN formation is not yet understood and it has not been proven that FA actually reaches the basal layer of the mucosa in sufficient amounts to induce MN (as a consequence of unrepaired DNA damage). Our negative results in a rat inhalation study (Speit et al., 2011) and our in vitro co-cultivation experiments (Neuss et al., 2010a) argue against such a possibility. The positive results of the human studies with exfoliated cells just suggest an association between FA exposure and increased MN frequencies. They do not prove a causal relationship and do not offer a scientific explanation for such an effect. A critical look at the data base of these studies questions the reliability of the results. For example, positive results are reported for buccal cells but negative for nasal cells in the same study (Suruda et al., 1993). However, due to the higher level of exposure of the nose and the morphology of the nasal epithelium, positive effects should rather be expected in nasal than in buccal cells. Other studies report positive results in buccal or nasal cells and also in lymphocytes of the same subjects (Suruda et al., 1993; Ye et a1.,2005; Viegas et a1.,2010). Considering the lack of systemic availability of FA (see the discussion on distant site effects), such results do not support each other but are rather implausible. Such results cast doubt on the role of FA as a causative agent. Other factors (chance findings, confounders, psychological factors) have to be considered. Finally, only few studies are available which investigated the induction of MN in buccal or nasal cells after defined exposure to strong mutagens (e.g. cancer patients after chemotherapy). The results obtained lack consistency and neither a clear dose-response nor time kinetics for MN formation could be derived from these studies (for review see Speit and Schmid, 2006). This means that no reliable data are available for a study group which might be	the OECD guideline for the *in vivo* micronucleus test and may in part compensate these limitations but it is not possible on the basis of this assay to exclude a potential role of mutagenicity in the mode of action of induction of nasal tumours observed in rats. Besides, the capacity of formaldehyde to induce genotoxic effects *in vivo* at the site of contact was identified by oral route in the GI tract by Migliore 1989 and in the lung by inhalation in Dallas 1992. In this study, 50 cells per animal were analysed both in the bone marrow and in the pulmonary macrophages and it does not indicate	**cells at distant sites of exposure:** We agree with the conclusion that genetically distant site effects after inhalative exposure are highly unlikely. **Experimental data; *in vivo* on germ cells:** It has been shown that formaldehyde has no relevant systemic availability to reach the gonads for inducing germ cell mutations. We agree with the conclusion that there is no basis for classification of formaldehyde as germ cell mutagen. **Human data at the site of contact:** It was reported on increased micronuclei frequency in buccal and nasal mucosa cells in several publications as well on negative results.

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		accepted as a "positive control". Interestingly, an international expert group (the Human Micronucleus Project; "HUMN") started an initiative ("HUMN(XL)") for the standardization and validation of the MNT with buccal cells in 2009, i.e., nearly 20 years after some of the FA studies were published (Bonassi et al., 2009). This expert group now began to identify test variables which influence the MN frequency and to perform validation trials. Without any standardization and validation, a genotoxicity test is unsuited for regulatory purposes. In summary, the published positive results after FA exposure might suggest that FA induces MN in exfoliated mucosa cells ("Indication of local genotoxicity in exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal mucosa cells in several studies"). However, it is premature to use these results for the evaluation of the mutagenic potential of FA. At present the MNT with exfoliated cells is a nice scientific "toy" but not a useful tool for the classification of mutagens / carcinogens and risk assessment (Speit and Schmid, 2006). **Human data; in humans at distant sites** Several biomonitoring studies reported positive results for genotoxic effects in peripheral blood of (groups of) subjects exposed to FA. Again, these tests show associations between FA exposure and effect. Biological significance of such a result is supported in a few studies by a positive correlation between FA exposure and the genetic effect measured. However, this is no proof and without any mechanistic explanation chance findings are likely. Primary DNA damage (DPX) was measured by the comet assay (Costa et al., 2008; Jiang et al., 2010: N.B. This study was published 2005 in Chinese; first author: Yu). However, increased DNA migration was measured whereas FA is a strong crosslinker (the strongest ever tested in the comet assay) and should cause reduced DNA migration. Increased DNA migration after FA exposure (which has also been reported in a few *in vitro* studies) seems to be due to assay variability or a test artefact. It is a general problem that the comet assay is used by many groups but not all have enough experience and competence to produce reliable results. This positive result is also not consistent with the clear negative result obtained in our inhalation study with rats. Furthermore, there is no explanation how leucocytes are sufficiently exposed to FA to show such DNA effects. With regard to the positive results in cytogenetic tests (i.e., chromosome aberration test, MNT, SCE test) with cultured lymphocytes two questions are	an apparent specific difficulty to analyse macrophage chromosomes. A statistically significant effect was identified despite the low number of cells analysed (100 cells per animal included in the OECD guideline) and the high background frequency of chromosomal aberrations. It is also noted that in the lung a negative Comet assay was reported in Neuss 2010c but a positive and dose-related effect was identified in Sul 2007. The capacity of formaldehyde to induce genotoxicity *in vivo* at the site of contact is therefore identified in Migliore 1989 and Dallas 1992.	Although the positive results indicate a possible mutagenic effect we agree with the conclusion that it is premature to use the conflicting results for the evaluation of the mutagenic potential of formaldehyde. The main reasons are the lack of standardization of the micronucleus test with extrafoliated cells and the fact that no data are available from a study group which can be used as a 'positive control'. **Human data at distant sites (and conclusion):** According the current state of knowledge formaldehyde is not systemically available in such a quantitative order of magnitude to induce genotoxic/mutagenic

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		unanswered: (1) How (where and when) are lymphocytes sufficiently exposed? (2) Do (potentially) induced lesions persist in culture to produce the cytogenetic effect? I have discussed these aspects in one of our publications (Schmid and Speit, 2007) but these scientific arguments have not yet been adequately perceived by the scientific community. My concerns are the following: The cytogenetic tests measure genetic effects which mainly occur in vitro during the cultivation of lymphocytes as a consequence of persisting DNA damage. It is not known how lymphocytes are exposed to FA *in vivo* and the DNA is sufficiently damaged. If they were damaged, it cannot be explained how the cytogenetic effects are induced in vitro. We and others have shown that FA-induced DPX are repaired in all mammalian cells. Although lymphocytes may have a lower DNA repair capacity than other cell types, DPX are efficiently removed in cultured lymphocytes before the cells start replication (Schmid and Speit, 2007). The induction and detection of cytogenetic effects requires the presence of a certain amount of damage as demonstrated by our carefully performed in vitro experiments with human blood cultures. However, due to the relative low exposure to FA and the known toxicokinetics of FA, these requirements cannot be met in human biomonitoring. As long as we do not have a scientific explanation for the positive effects reported in human biomonitoring studies but convincing evidence that FA is not a systemically available mutagen (Speit et al., 2009; Lu et al.,2010; Moeller et al., 2011) one should be very reluctant in using these human studies for the classification of FA as a mutagen / carcinogen. The fact that several studies reported such positive effects is not a scientific argument for an exposure-related effect - other factors (study design, psychological expectations, confounder, chance findings) may be more important and cannot be ruled out. In summary, several studies suggest genotoxic effects in peripheral blood of subjects exposed to FA by inhalation. It is generally accepted that these results (associations between exposure and effect) cannot be explained - they just exist. There are strong scientific arguments (Schmid and Speit, 2007) and there are convincing experimental data from animal studies (see above) which question the plausibility and reliability of the human studies. The assessment of the genotoxic / mutagenic potential of chemicals for regulatory purposes has always primarily been based on standardized test systems and studies performed according to internationally accepted guidelines. These studies	**Experimental data; *in vivo* on somatic cells at distant sites of exposure** We agree that experimental data provide no evidence of a genotoxic effect of formaldehyde at distant sites of exposure. **Experimental data; *in vivo* on germ cells** We agree that experimental data provide no evidence of a genotoxic effect of formaldehyde in the germ cells relevant for classification. **Human data; in humans at the site of contact** Several studies report induction of micronuclei in nasal or buccal cells of subjects exposed to	effects at the distant site. For primary DNA damage (DPX) as well as for induction of chromosomal aberrations, micronuclei and SCE's in human lymphocytes no scientific explanations are available.

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		clearly show that FA does not induce mutations at distant sites. There is no scientific justification for qualifying this assessment because of questionable human studies. **Conclusions** The assessment of the mutagenic potential of chemicals has always been based on comprehensive testing in standard mutagenicity tests (*in vitro* and *in vivo*) following international guidelines for genotoxicity / mutagenicity testing. Besides the quality of the test performance and the reliability of the result, the plausibility of the findings has to be considered. FA has been extensively studied for its genotoxic and mutagenic potential. There is no doubt that FA is mutagenic *in vitro* in directly exposed proliferating cells. *In vivo* mutagenicity can be expected at the site of first contact when the target cells for mutagenesis are sufficiently exposed. At present we do not have reliable mutagenicity data to show that cells of the basal layer of the buccal or nasal mucosa are exposed by FA to a sufficient amount and unrepaired DNA damage leads to mutations in replicating cells. The published human studies are not scientifically sound enough for a reliable assessment of FA-induced local mutagenic effects. It is still unknown whether mutations in the nasal epithelium actually contribute to carcinogenesis. FA does only induce genotoxicity at the site of first contact and is not systemically available in a sufficient amount to induce genotoxicity and mutagenicity at distant sites. This has been clearly demonstrated in appropriately performed animal experiments. Positive human data lack plausibility and should not be considered for the classification of FA as a mutagen and potential carcinogen. Because FA is not a systemically available somatic cell mutagen, germ cell mutagenicity can virtually be excluded and any classification as a germ cell mutagen seems to be scientifically unjustified. *End of attachment 1*	formaldehyde. These positive results were observed in populations exposed in different settings such as industrial plants and embalming and anatomy/ pathology laboratories and both in studies comparing exposed and control groups and in studies investigating pre- and post-exposure frequencies in exposed subjects. However, the small size of the investigated population, the potential biais and confounders as well as the lack of standardisation of these assay do not allow to draw a conclusion of a causal relationship with formaldehyde in human at the site of contact but	

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			is considered as an indication of such an effect that bring a supportive evidence in the weight of evidence. **Human data; in humans at distant sites (and conclusion)** We note the following elements: Regarding Comet assay, although we take note of the reservations made regarding the crosslinking effect of FA and reliability of the results, the study by Zeller 2011 and co-authored by Dr Speit reported equivocal results in the Comet assay in the peripheral blood of exposed volunteers. The crosslinking effect of FA may also in part mask the clastogenic effect	

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			of FA. The absence of understanding how a genotoxic effect can be induced at distant site by formaldehyde is important in the weight of evidence but should not completely dismiss the observed results. However it is also observed that such effects at distant sites were not identified in experimental animals and altogether, we consider that the genotoxic effects at distant classification are not sufficiently convincing but a category 2 is justified on the basis of the genotoxic effect at the site of contact.	
12/12/2011	Germany/ MSCA	See attached document *ECHA Comment: The attachment 'DE-MSCA_Comment on Formaldehyde.doc' - Section Mutagenicity is copied below. Attachment No.3* **Mutagenicity:**	*comment: comments have been numbered to facilitate MSCA responses.*	*Comments have been numbered to facilitate MSCA responses.* [1] We are of the

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		[1] Page 10/11, 3rd paragraph of section 2.2: In addition to the information provided, there is evidence for germ cell mutation from intra-peritoneal administered formaldehyde in male albino rats (Odeigah 1997). According to the Guidance to Reg (EC) No. 1272/2008 classification as a Category 2 mutagen can - regardless of the presented evidence for local mutagenicity - already apply if only intraperitoneal *in vivo* tests show mutagenicity/genotoxicity and the negative test results from the *in vivo* tests using other routes of application are plausible. [2] Page 19, 5th paragraph of section 4.1: It is noted that Casanova (1989) reported DPX in rat nasal mucosa already from the lowest tested dose of 0.38 µg/L (x 6 h). The authors described a non-linear increase of DPX formation with increasing exposure and estimated that half-saturation of metabolic detoxification would occur at around 3µg/L. [3] Page 83, first paragraph: Neuss 2010c cannot be regarded reliable with regard to micronuclei induction as the positive control failed to induce micronuclei. [4] Page 83, 5th paragraph: Concerning the studies by Lu et al. 2010, 2011, Moeller et al. 2011, DNA adducts were only determined after single (6 h) or short-term (6h x 5 days) exposure to formaldehyde and are, therefore, not contradictive to epidemiological findings. [5] Page 83, 5th paragraph: The reliability of the report by Speit et al. (2009) may be considered limited. It is noted that the duration between the end of inhalative exposure and blood sampling was not specified. DPX in lymphocytes may have been repaired to a level below the detection limit by the time of analysis. Consequently, the outcome of the *in vivo* comet assay may be influenced by the time of sampling. Thus, some uncertainty is associated with the present study, as the time of sampling in relation to the end of exposure to formaldehyde has not been detailed. Moreover, blood samples from the present study were also used to perform two other *in vivo* genotoxicity tests apart from the comet assay: a sister chromatid exchange (SCE) test and a peripheral blood micronucleus test (MNT), both of which also yielded negative results. Positive controls were tested following oral dosing. It should be taken	[1] The study by Odeigah (1997) has been described in section 4.9.1.2.3 of the CLH report and is discussed in section 4.9.3. Because of the intra-peritoneal route of exposure, this study is not considered relevant to detect an effect on germ cell via 'normal' routes of exposure and to justify a category 1B. However, we agree that it brings supportive evidence of the capacity of formaldehyde to induce genotoxicity locally and support the classification as a category 2 mutagen. [2] Noted. This is reflected in the description of the study in section 4.9.1.2.1.	opinion that the increased numbers of sperm head abnormalities as well as dominant lethal effects after intra-peritoneal injection of FA to male rats (Odeigha et al., 1997) are not fully reliable. Due to the lack of positive controls, the study was not taken into account for supporting justification of Muta Cat. 2 classification. [2] Noted. [3] Noted. This is reflected in the description of the study in section 4.9.1.2.1. and in the discussion on page 84. [4] Noted. [5] In Speit et al. (2009), blood sampling is reported

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		into account that no other toxic effects were reported except of lower body weight gain at 10 and 15 ppm. This is in contrast to other studies. For example, frequent face washing, lacrimation, nasal discharge etc. were observed during the first four weeks of inhalation exposure at 15 ppm (Kamata et al. 1997). Other studies demonstrated effects on the nasal epithelium under similar conditions (e.g. Andersen et al. 2008[6], Monticello et al. 1991[7]). [6] Page 83, last paragraph (Page 84 ctd.): Although with some methodological limitations (e.g. purity not specified), Gules and Eren (2010) showed evidence of an effect of formaldehyde in testicular tissues of male Sprague Dawley rats following inhalation of 6 ppm of formaldehyde (8 h/d; 7 d/week, 5 weeks). This may indicate a potential for effects at distant sites, supporting classification as Muta Cat. 2. [7 Page 84, 1st paragraph concerning positive results obtained after intraperitoneal application: Please refer to the comment regarding Page 10/11. According to the Guidance to Reg (EC) No. 1272/2008 Chapter 3.5.2.4 "classification as a Category 2 mutagen would generally apply if only intraperitoneal *in vivo* tests show mutagenicity/genotoxicity and the negative test results from the *in vivo* tests using other routes of application are plausible." **Comparison with criteria:** [8] Page 85 f, concerning CLP guidance which stated that "…, it may be difficult to reach a decision on whether or not to classify in the case where there are positive *in vivo* data from at least one *in vivo* test using intraperitoneal application but (only) negative test data from (an) *in vivo* test(s) using oral, dermal, or inhalative application. In such a case, it could be argued that mutagenicity/genotoxicity can only be shown at internal body substance concentrations which can not be achieved using application routes other than intraperitoneal." This must not be interpreted as a reason for non-classification, but as the acknowledgement that the sensitivity of the testing	[3] Noted. This is reflected in the description of the study in section 4.9.1.2.1. and in the discussion on page 82/83. [4] The studies by Dallas 1992 (up to 15 ppm for 8 weeks) and Speit 2009 (up to 15 ppm for 4 weeks) investigate genotoxicity at distant sites with repeated exposures and also reported negative results. [5] In Speit 2009, blood sampling is reported to take place at the end of exposure and analyses were performed 4h after	to take place at the end of exposure. The blood samples for the comet assay and for the SCE test were stored on ice and analyses were performed about 4h after blood sampling. The blood samples for the micronucleus test were fixed in ultra-cold methanol and stored at -75°C until the analysis. It is highly unlikely that the result of one of the tests was influenced significantly by the sample preparation. [6] The publication of Gules and Eren (2010; Asian-Aust. J. Anim. Sci. 23 (11): 1412-1420) is not relevant for supporting the classification as Muta Cat. 2.

[6] Andersen ME, Clewell HJ 3rd, Bermudez E, Willson GA, Thomas RS. 2008, Genomic signatures and dose-dependent transitions in nasal epithelial responses to inhaled formaldehyde in the rat. Toxicol Sci. Oct;105(2):368-83.

[7] Monticello, T. M.; Miller, F.; Morgan, K. 1991, Regional increases in rat nasal epithelial cell proliferation following acute and subchronic inhalation of formaldehyde. Toxicol Appl Pharmacol, 111: 409-421

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		methods is limited. *End of attachment no. 3 – Section Mutagenicity*	blood sampling. Although DPX may have been repaired to a certain extent, a complete repair is not expected after such a short time. Besides, it is noted that it does not impact the overall assessment of a potential effect at distance site that is mainly based on the lack of convincing evidence in experimental animal. [6] No bibliographic reference was given for the study by Gules and Eren (2010) and it was not retrieved under Pubmed; Therefore, the relevance of the study cannot be assessed by FR.	because changes in testicular tissues, a parameter of reproductive toxicity, were evaluated. [7] The increased number of sperm head abnormalities as well as dominant lethal effects after intra-peritoneal injection of formaldehyde to male rats (Odeigha et al., 1997) are not fully reliable because positive controls are lacking. The results do not support classification as a Cat. 2 mutagen. [8] see response to comment [7]

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			[7] We agree that positive results on germ cells by intra-peritoneal route also support classification in category 2 and a reference to the guidance has been added in the CLH report. [8] see response to comment [7].	
14/12/2011	Belgium/ Formacre	See attached report, p35-p41. Classification for mutagenicity always refers to germ cell mutagenicity. Due to the high reactivity of FA, DPX, DNA adducts and DNA-DNA cross links have only been observed in the nasal tissue of rats after inhalation. Furthermore, inhalation of FA does not lead to an increase of its blood concentration. Therefore FA will not reach the germ cells and a classification for (germ cell) mutagenicity is not warranted. In the CLH report two studies are specifically mentioned as giving support to a mutagenicity cat. 2 classification: Dallas et al. (1992) claimed that chromosomal aberrations in lung lavage cells are induced after inhalation exposure. But this finding could not be reproduced in a recent inhalation study in which neither MN nor DNA strand breaks, alkali-labile sites or DPX were induced in lung lavage cells. This study must be given precedence over the Dallas study.	This document is similar to the document submitted by APEQ/Lubelia Penedo (attachment 12) and the full comment was pasted in the present table. Please refer to the response to this comment.	Noted.

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		Migliore et al. (1989) reported MN formation in the gastric mucosa after oral application at a highly cytotoxic dose level leading to hyperemia and hemorrhage. This study can by no means be compared to the inhalation exposure situation. In conclusion there is no reason to classify FA as a cat. 2 mutagen. *ECHA Comment: The document: 'formacare submission.zip' was submitted as a separate attachment. Attachment No.6 . which is the same document submitted from Portugal/Lubelia Penedo/APEQ-Protuguese Chemicals Association (attachment no. 12 file name 'Scientific response to French CLH report on formaldehdye.pdf')*		
15/12/2011	Denmark/MSCA	Mutagenicity Numerous studies have shown that formaldehyde causes somatic cell mutagenicity in vivo at the site of contact. Furthermore, human studies have also shown an indication of a local genotoxic effect of formaldehyde at the site of contact. Fewer studies of germ cell mutagenicity in vivo are published compared to studies on somatic cell mutagenicity in vivo. The results of these studies are inconsistent and inconclusive and more studies are needed to make firm conclusions. However, based on the available studies, it cannot be excluded that formaldehyde by inhalation may also cause germ cell mutagenicity. Therefor based on the above mentioned information, we support classification with Muta 2 H341 as the criteria for this classification is fulfilled.	The support for classification Muta 2 is noted.	The support for classification Muta 2 is noted.
15/12/2011	The Netherlands/ RIVM	We agree that there is clear evidence for local mutagenicity of formaldehyde fulfilling the criteria for classification as Muta cat 3; R68 and Muta 2; H341. We also agree that it is unlikely that formaldehyde can have a mutagenic effect on the germ cells because it is unlikely that formaldehyde can reach the gonads.	The support for classification Muta 2 is noted.	The support for classification Muta 2 is noted.
15/12/2011	Sweden/ MSCA	KemI agrees with France that genotoxic effect of formaldehyde in somatic cells at the site of contact is relevant to human health and that the experimental (and human?) evidence available do warrant classification of the substance in Category 2 for CLP germ cell mutagenicity.	The support for classification Muta 2 is noted.	The support for classification Muta 2 is noted.
15/12/2011	United Kingdom/	With reference to the last paragraph in section 4.9.4, we agree that, in some cases (for example, for substances for which there is no carcinogenicity data	We agree that there is no	The rapporteurs in their opinion

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
	MSCA	available), classification of a 'site-of-contact' mutagen in category 2 may be warranted in order to warn of a substance's carcinogenic potential. However, we believe application of this approach must be considered on a case-by-case basis and may not appropriate for formaldehyde, whose carcinogenic potential has been extensively investigated. Since formaldehyde is already classified as a carcinogen, we would prefer mutagenicity discussions to focus on formaldehyde's ability to cause germ cell mutations. We are concerned classification as a suspected germ cell mutagen, in addition to a carcinogen would be misleading, given many of the positive in vivo somatic cell studies were in tissues (i.e. nasal respiratory epithelium) that are not good surrogates for germ cells. The results of studies in more suitable tissues (i.e. bone marrow) were negative.	convincing evidence of a potential effect in germ cells. However, the CLP criteria allows to our understanding to classify in category 2 even where there is no specific concern for germ cell considering the potential impact on carcinogenicity. This classification is therefore fully relevant for formaldehyde in relation to assessment of carcinogenic effects of the substance (see also response to APEQ comments below).	document emphasise that there is no convincing evidence of a potential effect in germ cells after relevant inhalation exposure of formaldehyde. The DS's proposal is agreed on, that CLP criteria allow for classifying in category 2 even where there is no specific concern for germ cells considering the potential impact on carcinogenicity.
15/12/2011	Portugal/ APEQ- Portuguese Chemicals Association	Please see the Zip file Scientific response to French CLH report formaldehyde.pdf, pgs 21, 35 *ECHA Comment: the document 'FORMALDEHYDE RESPONSE.zip' was submitted as a separate attachment. Attachment No.12. 'Scientific response to French CLH report on formaldehdye.pdf' , page 21-41 are copied below.* **4.c. Mutagenicity: it is recognized that genetic events are central in the**	The following comments can be made: On section 4.c.1, it should also be raised that at the site of contact, induction of	*Comments on section 4.c.1:* We agree to the conclusion that there is a clear evidence for induction of genotoxic effects (DPX, DNA adducts and DNA-DNA cross

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		overall process of cancer development Genotoxicity/mutagenicity is an important criterion to be taken into account for carcinogenicity classification. Therefore the basic data are summarized here. Special emphasis is given to the interpretation of mutagenic effects observed at the site of direct contact, especially in nasal and buccal cells of humans. Such findings would be important for the interpretation of the induction of tumors in the upper respiratory tract. The classification for mutagenicity per se is addressed in a separate chapter. *Gentoxicity/mutagenicity in vitro:* FA induced gene mutations in bacteria but these effects cannot be directly translated to mammalian systems because bacteria are lacking histones and therefore the predominant genotoxic effect in mammalian cells, i.e. DPX formation, is not possible in the same manner. Gene mutations in mammalian cells are of minor importance, and FA primarily leads to clastogenic effects via DPX formation generally associated with cytotoxicity (Merk and Speit, 1998; Speit and Merk, 2002). Furthermore, there is an indication for a practical threshold for induction of MN in vitro (Speit et al., 2007). As regards genotoxicity, the standard alkaline comet assay generally is negative (Speit et al., 2007). Similar to MN induction, in vitro studies showed that SCE induction is associated with cytotoxicity and there is an indication for a practical threshold under i n vitro conditions (Speit et al., 2007). SCE inducing DNA lesions are rapidly repaired (Neuss and Speit, 2008). DPX are rapidly repaired in various cell lines (Cosma and Marchok, 1988; Schmid and Speit, 2007; Speit et al., 2007, 2008). Co-cultivation experiments with the endpoints of SCE (Neuss and Speit, 2008) and DPX (Neuss et al., 2010) showed that FA after having entered a cell is not passed on to neighbor cells. *Systemic genotoxicity/mutagenicity in vivo:* such systemic effects might be related to the induction of systemic tumors like leukemia. But as leukemia is not a criterion taken forward in the CLH dossier for carcinogenicity classification, reports on systemic genotoxicity/mutagenicity are only briefly summarized here. In vivo animal studies did not show systemic genotoxic (SCE, DNA strand breaks, DPX) or mutagenic effects (MN, chromosomal aberrations) after oral or inhalation exposure (Jensen et al., 1982; Natarajan et al., 1983; Kligerman et al., 1984; Dallas et al., 1992; Morita et al., 1997;	chromosomal aberrations in the lung was observed at the highest dose in Dallas 1992 and induction of micronuclei in the GI tract by oral route in Migliore 1989. It was also supported by the induction of mutagenic effects in the germ cells by intraperitoneal route and justifies a classification Muta 2. It is recognised that no mutagenic effects was detected in experimental animals in the nasal epithelium, which is the site of tumours. But only one study investigates this tissue for mutagenicity (Speit 2011). It is discussed in further details in the response to the comments of Guenter Speit why	links) by formaldehyde at the site of contact (nasal mucosa). It should be noted that there is no clear evidence for the induction of mutations in the nasal epithelium cells after inhalation of formaldehyde until now. A recent study by Speit et al. (2011) shows no increased MN frequencies in nasal epithel cells of rats but some limitations of the study have to be discussed (e.g. no established test system; no valid positive control). The positive results of in vivo studies on mutagenic effects at the site of contact (other cells than nasal epithelium cells) should be interpreted with care because they include methodical limitations. Dallas et al. (1992)

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		Speit et al., 2009). Inhalation exposure to exogenous [13CD2]FA did not lead to an increase of DNA adducts and DNA-DNA cross links in all tissues investigated far off the site of first FA contact. But in all of these tissues such DNA modifications caused by endogenous FA were observed (Lu et al., 2010). Similarly, no DNA adducts caused by exogenous FA were found in the bone marrow of exposed monkeys, but adducts cause by endogenous FA were clearly identified (Moeller et al., 2011; Lu et al., 2011a). Systemic genotoxic and mutagenic effects are reported for exposed humans in some studies (with other studies being negative). By a weight of evidence evaluation and taking account of mechanistic information these data do not allow the conclusion that FA leads to systemic (Heck and Casanova, 2004; BfR, 2006; Speit et al., 2009) genotoxic or mutagenic effects in exposed humans. **4.c.1. Local genotoxicity in vivo (experimental animals):** genotoxic effects caused by FA at the site of first contact are known since decades and have recently been confirmed by a highly sensitive MS method. DPX have been demonstrated in nasal tissue at the predilection sites for tumor formation after inhalation exposure in rats (Casanova et al., 1989) and in addition in monkeys (Casanova et al., 1991) with a non-linear dose response relationship. DPX are rapidly repaired in vivo (Casanova et al., 1994). Point mutations of the p53 gene were identified in nasal carcinomas (Recio et al., 1992) but it was later demonstrated that FA per se does not induce such mutations in the p53 or K-ras gene (Meng et al., 2010). Inhalation exposure to exogenous [13CD2]FA led to an increase of DNA adducts and DNA-DNA cross links in the nasal epithelium in rats(Lu et al., 2010, 2011, 2011a) and to DNA adducts in monkeys (Moeller et al., 2011). A highly non linear dose response relationship was described for the dG DNA adduct found in rat nasal tissue after inhalation exposure to exogenous labelled FA. At exposure levels of 0.7, 2.0, 5.8, 9.1 and 15.2 ppm the dG adducts derived from exogenous FA amounted to 1, 3, 20, 60 and 260 % of those formed endogenously (Lu et al., 2011, 2011a). **4.c.2. Local mutagenicity in the upper respiratory tract (experimental animals and humans):** The question of local mutagenicity in the upper respiratory tract may be of major importance for a decision on carcinogenicity classification of FA. There are positive and negative studies for micronuclei in buccal or nasal cells of humans exposed to FA. These data are taken as supportive evidence in the CLH report for the classification of FA as	this study is not considered sufficient to exclude a potential role of mutagenicity in the mode of action of induction of nasal tumours observed in rats. It therefore cannot be concluded as in section 4.c.2 (page 24) that positive findings in humans are contradicted by animal studies that allow detecting a mutagenic effect of formaldehyde at the site of contact. On induction of MN in nasal or buccal cells in humans discussed in section 4.c.2 it is noted that 1/the evidence that FA is not passed on from on cell to a neighbour cell is not sufficient to exclude a potential contact, e.g. a direct contact of FA with dividing	reported on a marginal but statistically significant increase in chromosomal aberrations in the broncho-alveolar lavage cells from rats after inhalation of FA (limitations: high background frequency of chromosomal aberrations; no positive control). Migliore et al. (1989) informed on the induction of micronuclei in cells of the gastro-intestinal epithelium of rats treated orally with FA (limitations: effect was observed in conjunction with signs of severe local irritations; questionable relevance of the positive control). *Comments on section 4.c.2:* As a result of the discussion on indication of local genotoxicity in

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		carcinogenic cat 1A as stated on p. 11: "Indication of local genotoxicity in exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal mucosa cells in several studies." Therefore these findings will be discussed here in detail. Inhalation exposure may affect both buccal and nasal cells, the latter even to a larger extent, as FA acts primarily on the upper respiratory tract. But studies investigating MN in workers must be carefully evaluated because many factors are difficult to control, like coexposure to other chemicals or life style of workers and control subjects. Above all, the study protocols for nasal and buccal cells are by no means yet standardized or validated. This is taken into account by an assessment of BfR (2006) and Appel et al. (2006) concluding that these studies are not sufficiently standardized, not fully or sufficiently reliable and the results are difficult to interpret. Similarly, a review of Speit, Schmid (2006) of studies specifically related to this endpoint cautioned that the data may suggest an increase in MN frequencies, but as there are methodological shortcomings and limited documentation the local genotoxicity of FA in humans can presently not be fully assessed. Thus, two independent reviews have questioned the reliability of the database on local MN induction in workers. First of all, the positive findings in humans are contradicted by an animal study with high, well defined exposures. In rats exposed by inhalation up to 15 ppm over 4 weeks no increase in MN frequency was found in nasal epithelial cells (Speit et al., 2011). There is no reason to assume that the nasal tissue of rats is much less sensitive to the action of FA than that of humans. In the following the studies on micronuclei (MN) formation in exfoliated nasal and buccal cells of humans will be assessed in detail to come to a comparative weight of evidence evaluation. Thereby the following more general factor should be taken into consideration: 1. The histological structure of the epithelium: the epithelium of the buccal mucosa is about 40-50 cell layers thick, while the sublingual and respiratory	basal cells. FA is a small water-soluble molecule and may diffuse towards deeper layers of the epithelium. This may be particularly true during peak exposure overwhelming local defences. The methodological limitations described in points 2, 3, 4 and 5 on pages 24-25 are acknowledged and support that a firm conclusion cannot be drawn on the basis of human data for local mutagenicity. Besides, the criticism commented on page 25 regarding the small number of subjects in Speit 2007 is correct for this study as stated in the CLH report and is also more generally	exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal cells, we conclude that the positive results are not sufficient to prove an induction of local mutagenicity of FA on the upper respiratory tract. Although the positive results indicate a possible mutagenic effect we agree to the conclusion that it is premature to use the conflicting (positive/negative) results for the evaluation of the mutagenic potential of formaldehyde. Consequently, these data should not be used as supporting argument for classification of formaldehyde. *Comments on section 5a/c:* A statement on germ cell

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		mucosa have fewer cell layers (Speit, Schmid, 2006). As it has been shown in vitro that FA is not passed on from the cell of primary contact to neighbour cells (Neuss and Speit, 2008; Neuss et al., 2010) it is not very likely that FA after inhalation may reach the dividing basal cells in which MN may be induced. 2. The regeneration time of the epithelium: the time for buccal cells to emerge from the basal cell layer and exfoliate is estimated to be about 7-16 days with a peak of 8-21 days (Speit, Schmid, 2006) or 7-10 days (Titenko-Holland et al., 1996), while the estimated maximum lag time for nasal cells was estimated to be 16 days (Titenko-Holland et al., 1996). Therefore, Titenko-Holland et al. (1996) proposed to use besides a cumulative 90 day exposure estimate a cumulated dose only over the last 7-10 days before sampling as dose metric. But as the data for lag times are limited and lack consistency it is premature to give general recommendations for the optimal time point for MN analysis. Therefore in the comparative tables below different exposure metrices are given and the cumulative exposure over 2 weeks is used as an appropriate metrix to compare the different studies with each other. 3. A sufficient number of cells should be scored; according to Titenko-Holland et al. (1996) and Speit, Schmid (2006) about 1500-2000 cells are necessary. 4. Differences in scrapings may affect the results as MN are less frequent in superficial layers of the oral mucosa (Speit, Schmid, 2006). This may especially play a role when scrapings are done at different times and particularly by different persons. 5. Background frequencies: according to Speit, Schmid (2006) the "Human Micronucleus Project" reported average MN frequencies in the normal human population of 1-3‰ with no significant variations between different types of exfoliated cells. But within the studies to be discussed, several control frequencies were clearly outside this range. In the assessment of MN in exfoliated cells by the CLH report (p. 84) it is stated that the negative results in the two volunteer studies may be due to - the lower exposure in particular to peaks - and to the small number of subjects. The following tables give an overview of the most relevant parameters of the studies investigating MN in epithelial buccal or nasal cells. Many of these	raised as an additional difficulty to interpret the whole human studies. Regarding the comparison of the levels of exposure and especially the peaks, it is emphasised that exposure to peak in Speit 2007 was limited to 1 ppm for only 15 minutes. The peak was repeated 4 times in the day on two days during the 10-day exposure period. Peak exposure is not reported in many of the other studies but most of them were performed in anatomy and pathology laboratory (Ying 1997, Burgaz 2001 and 2002) or in morticians (Suruda 1993, Titenko-Holland 1996). IARC (2006) reports an upper	mutagenicity can be made only for substances that have a sufficient systemic availability to reach the germ cells. This does not apply for formaldehyde. Following the current state of knowledge of intrinsic toxicity it can be assumed that formaldehyde doesn't reach the germ cells but due to its high reactivity formaldehyde reacts with tissues of first contact. For such substances the Guidance document for CLP states in section 3.5.: 'It is also warranted that where there is evidence of only somatic cell genotoxicity, substances are classified as suspected germ cell mutagens. Classification as a suspected germ cell mutagen may also

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		studies were included in the review of Speit, Schmid (2006) but the study of Kitaeva et al. (1996) was excluded because the cells from students were scored after a primary one-time contact with FA and positive findings were obtained 24-48 h thereafter (this time span is too short considering the kinetics of MN formation). Further comments on the studies listed in the table: *Ballarin et al. (1992):* workers in a plywood factory, the exposure levels were given as 0.1 and 0.39 mg/m³ (0.08 and 0.32 ppm). Assuming that the workers worked 8 h/d, 5 d/week this would lead to a cumulative exposure over the last 2 weeks of 6.4 and 25.6 ppm x h. There were two groups of workers with a marked difference in exposure: 7 warehouse workers: mean TWA (8h) 0.32 ppm; 8 workers in sharing/pressing/sawmill: mean TWA (8h) ~0.1 ppm. While for both groups combined there was a significant difference in MN to the control group (0.90 vs 0.25 %o, $p<0.01$), there was no significant difference within these two exposure subgroups (0.32 ppm: 0.97 %o; 0.1 ppm: 0.74 %o). The close resemblance of MN frequencies in both subgroups with a clear difference in exposure level (no dose response relationship) remained unexplained. But it is to be noted that all workers were exposed to wood dust at concentrations varying between 0.11 and 0.73 mg/m³ leading to the possibility that wood dust might have been a major factor for induction of MN in both groups. **Studies of MN in buccal cells (positive studies are marked by a bold reference)**	range of exposures up to 16.7 ppm during embalming (most upper values reported around 4 to 10 ppm) and up to 20.3 ppm in anatomy laboratory (most upper values reported around 2 to 3 ppm). This confirms that the peak exposure in the volunteer studies is probably lower than in a professionally exposed populations. In conclusion, several studies report induction of micronuclei in nasal or buccal cells of subjects exposed to formaldehyde. These positive results were observed in populations exposed in different settings such as industrial	have implications for potential carcinogenicity classification. This holds true especially for those genotoxicants, which are incapable of causing heritable mutations because they cannot reach the germ cells (e.g. genotoxicants only acting locally, 'site of contact' genotoxicants. This means that if positive results in vitro are supported by at least one positive local in vivo, somatic cell test, such an effect should be considered as enough evidence to lead to classification in Category 2.' Following these criteria the proposed classification for formaldehyde as Muta. 2 is fully relevant. *Comments on section 5b:*

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Ref**	No of cells	Stain	Location scraping	Number of		Mean MN in %o (p)		Exposure (ppm)		
				Contr	Exp.	Contr	Expo.	TWA (h)	Peak	Cumul*
No92		A O	nr	34	28	3.4	7.6	0.1, 0.2, 0.3 (different factories)	nr	8-24
Su93	1500	F/FG	Cheek	29	29	0.046	0.60 (<0.05)	1.4 (125 min);0.3 (8h) estimated, range 0.15-4.3	nr	5
Ti96	561-4113	FISH	Cheek	19	19	0.6 (t) 0.1 (-)	2.0(t) (0.007) 0.9(-) (0.005)	Similar to Su93	nr	1.2
Yi97	~3000	Wright	Cheek	25	25	0.568	0.857 (<0.01)	0.41; 3h/d, 3d/wk	1.28	7.4
Bu02	3000	F/FG	Cheek	18	28	0.33	0.71 (<0.05)	2-4, 8 h/week	nr	32-64
Sp07	2000	DAPI	Cheek	21	21	0.95; 0.86	1.33; 0.94; 0.85; 0.44 (ns)	Up to 0.5, 4 h/d	1	13.5
Vi10	2000	F	cheek	85	30(f) 50(a)	0.13	f:1.27(<0.001) a:0.64(<0.005)	f: 0.21 a: 0.28	f: 0.52 a: 2.52	f:14.7 a:19.6
La11	2000	F	Cheek?	85	56	0.81	0.96 (0.002)	0.16	1.14	11.2

*: cumulative exposure over the last 2 weeks (ppm x h). If no details are given, the exposure duration for workers is assumed to be 8 h/d, 5 d/week over 2 weeks

**: references are given as the first two letters of the first author and the last two digits of the year of publication

nr: not reported. ns: not significant (t): total MN. (-): centromere negative MN

I T: inner turbinate. If T: inferior turbinate

F/FG: Feulgen / Fast Green. A O: acridine orange FISH: FISH with centromere probe

DAPI: DAPI/propidium iodide and fluorescence microscopy. F: Feulgen without counterstain

f: workers in a FA/FA resin factory. a: workers in a anatomy/pathology laboratory

plants and embalming and anatomy/ pathology laboratories and both in studies comparing exposed and control groups and in studies investigating pre- and post-exposure frequencies in exposed subjects. Although we consider that the small size of the investigated population, the potential biais and confounders as well as the lack of standardisation of these assay do not allow to draw a conclusion of a causal relationship with formaldehyde in human at the site of contact, it is considered as an indication of such an effect that bring a supportive evidence in the weight of evidence.

The conclusion that 'the toxicological profile does not warrant a classification for mutagenicity' (first paragraph) is not correct (see comments on section 5a/c).

The positive results of in vivo studies on mutagenic effects at the site of contact (other cells than nasal epithelium cells) should be interpreted with care due to their methodological limitations. Therefore the study of Dallas et al. (1992; induction of chromosomal aberrations in rats by inhalation of formaldehyde) and Migliora et al. (1989; induction of micronuclei in rats in the gastrointestinal tract by oral route) as well as the studies indicated local genotoxicity in

<table>
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Studies of MN in nasal cells (positive studies are marked by a bold reference)
<table>
<tr><th></th><th>No of cells</th><th></th><th>Location scraping</th><th>Number of</th><th></th><th>Mean MN in %o (p)</th><th></th><th>Exposure (ppm)</th><th></th><th></th></tr>
<tr><th>Ref**</th><th></th><th>Stain</th><th></th><th>Contr</th><th>Exp.</th><th>Contr</th><th>Expo.</th><th>TWA (h)</th><th>Peak</th><th>Cumul*</th></tr>
<tr><td>Ba92</td><td>6000</td><td>F/FG</td><td>l T</td><td>15</td><td>15</td><td>0.25</td><td>0.90 (<0.01)</td><td>0.08-0.32 (8h)</td><td>nr</td><td>6.4-25.6</td></tr>
<tr><td>Su93</td><td>1500</td><td>F/FG</td><td>lf T</td><td>29</td><td>29</td><td>0.41</td><td>0.50 (0.26, ns)</td><td>1.4 (125 min);0.3 (8h) estimated, range 0.15-4.3</td><td>nr</td><td>5</td></tr>
<tr><td>Ti96</td><td>394-5770</td><td>FISH</td><td>lf T</td><td>13</td><td>13</td><td>2.0 (t)
0.5 (-)</td><td>2.5(t) (0.2,ns)
1.0(-) (0.03)</td><td>Similar to Su93</td><td>nr</td><td>1.2</td></tr>
<tr><td>Yi97</td><td>~3000 ?</td><td>Wright</td><td>Septum</td><td>25</td><td>25</td><td>1.2</td><td>3.85 (<0.001)</td><td>0.41; 3h/d, 3d/wk</td><td>1.28</td><td>7.4</td></tr>
<tr><td>Bu01</td><td>3000</td><td>F/FG</td><td>l T</td><td>25~1.4</td><td>23</td><td>0.61</td><td>1.01 (<0.01)</td><td>2-4, 8 h/week</td><td>nr</td><td>32-64</td></tr>
<tr><td>Ye05</td><td>3000</td><td>Wright</td><td>septum</td><td>23</td><td>18</td><td>1.25</td><td>2.70 (<0.05)</td><td>0.8, 8 h/d, 6 d/wk</td><td>~1.4</td><td>76.8</td></tr>
<tr><td>Ze11</td><td>2000</td><td>DAPI</td><td>l T</td><td>41</td><td>41</td><td>0.21</td><td>0.27; 0.24; 0.24; 0.17 (ns)</td><td>Up to 0.7, 4 h/d</td><td>0.8</td><td>8.3</td></tr>
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For explanations see table on buccal cells

Norppa et al. (1992): this study is reported as an abstract only. Workers in a plywood factory, in a chipboard impregnation facility and in fibre glass production were investigated. Therefore at least for part of the workforce co-exposure to wood dust is to be assumed. Calculation of cumulative exposure was carried out as described for Ballarin et al. (1992) leading to a 2 week cumulative exposure of 8-24 ppm x h. The MN frequency in the control group is very high as compared to the other studies and the proposal of the "Human Micronucleus Project". Although the exposure at the 3 factories was clearly different, the same results were obtained for each factory separately (no dose response relationship). This may indicate to an unknown confounding co-exposure.
</td>
<td>It is noted that the summary reported in section 4.d relates to assessment of carcinogenicity. The criteria identified to justify a classification in category 2 relates to interpretation of experimental data and are not relevant in the case of discussion a category 1A for which human data are available (and supported by experimental data).

Section 5.a of the comment relates to the potential focus of the mutagenicity classification on germ cells mutagenicity. The CLP criteria however states in section 3.5.2.1 that "This hazard class is primarily concerned with</td>
<td>exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal mucosa cells should not to be considered for supporting the classification of formaldehyde as mutagenic.</td>
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		Suruda et al. (1993): study on mortician students during embalming course; the MN frequencies pre-course served as control value in comparison to the post-course value. The cumulative exposure over the whole course was calculated as 14.8 ppm x h. If it is assumed that 1/3 of all embalmings concentrated during the last 2 weeks of the course, a cumulative 2-week exposure of 5 ppm x h would be obtained. This value is taken as the relevant cumulative exposure. Only for buccal cells (not for nasal cells) a significant pre- vs post-course increase was noted, but the control value (0.046 ‰) was extremely low and only 2 students had any baseline MN, both females. Thus the increase during the embalming course is difficult to interpret. *Titenko- Holland et al. (1996):* follow up study of Suruda et al. (1993); unstained slides of the Suruda study were used for FISH centromere probe to differentiate between aneugenicity and clastogenicity. MN appeared to be mainly caused by clastogenicity. 2 exposure metrices were calculated: whole course cumulative as in the Suruda study and 7-10 day cumulative with the following results: buccal cells: whole course 14.8 ppm x h; 7-10 day: 1.2 ppm x h nasal cells: whole course 16.5 ppm x h; 7-10 day: 1.9 ppm x h The 7-10 day exposure is taken as relevant. Basically the results of Suruda were confirmed: the effect in buccal cells was significant for both total and centromere negative MN, while in nasal cells there was a significant post-course increase only for centromere negative MN. It should be noted that the quality of the slides might in some cases not have been sufficient, as only low numbers of cells could be scored (<1500 as recommended) for some subjects, although the average number of cells scored was in the range of the recommended 1500/subject. There was no correlation of the MN increase with both of the exposure metrices used. *Ying et al. (1997)*: students in an anatomy course over 8 weeks, the MN frequencies pre-course served as control value in comparison to the post-course value. Exposure 3 h/d, 3 times a week. The mean exposure of 0.41 ppm would give a cumulative exposure over the last 2 weeks of 7.4 ppm x h.	substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class." Besides the Guidance document for CLP states in section 3.5.1 that "It is also warranted that where there is evidence of only somatic cell genotoxicity, substances are classified as suspected germ cell mutagens. Classification as a suspected germ cell mutagen may	

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		Burgaz et al. (2001): pathology and anatomy staff analyzed for nasal cells. No appropriate local ventilation and no personal protection. Exposure assessment only by stationary measurement: 2-4 ppm. Exposure duration 8 h/week for 20 subjects, for 3 subjects only 2 h/week. This leads to a 2-week cumulative exposure for the majority of the subjects of 32-64 ppm x h. As only stationary measurements are available, the actual exposure of the subjects is very uncertain. *Burgaz et al. (2002) and erratum (2006)*: pathology and anatomy staff analyzed for buccal cells. By comparison of the exposure condition, the subjects were obviously drawn from the same working place as those studied by Burgaz et al. (2001). In addition a group of shoemakers was investigated without exposure to FA, but to relatively high concentrations of n-hexane (mean ~58 ppm), toluene (mean ~26 ppm) and methyl ethyl ketone (mean ~11 ppm). Although these solvents are generally thought not to lead to mutagenic effects, there was a statistically significant increase in MN frequency in the exposed shoemakers as compared to controls (0.62 vs 0.33 ‰). The anatomy workers were exposed to the same range of these solvents and in addition to FA. The mean MN frequency in this group (0.71 ‰) was very close to that of the shoemakers and also statistically significantly different from the control group. Thus, in principle it cannot be decided whether the MN were caused by FA or the other solvents. *Ye et al. (2005)*: this study on highly exposed workers in FA manufacturing (~0.8 ppm) and waiters exposed to low concentrations (~0.09 ppm) was already carried out in 1992. Exposures were determined by environmental monitoring. The exposure situations were as follows: Waiters: 5 h/d, 7 d/week leading to a 2-week cumulative exposure of 6.3 ppm x h Workers: 8 h/d, 6 d/week leading to a 2-week cumulative exposure of 76.8 ppm x h. While there was a statistically significant increase in MN noted for the workers in comparison to the control group, this was not found for the group of waiters.	also have implications for potential carcinogenicity classification. This holds true especially for those genotoxicants which are incapable of causing heritable mutations because they cannot reach the germ cells (e.g. genotoxicants only acting locally, "site of contact" genotoxicants). This means that if positive results *in vitro* are supported by at least one positive local *in vivo*, somatic cell test, such an effect should be considered as enough evidence to lead to classification in Category 2. If there is also negative or equivocal data, a weight of evidence	

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		Speit et al. (2007a): investigation on buccal cells in volunteers exposed over 2 weeks (4 h/d) at defined exposures of 0.15-0.5 ppm with peaks up to 1 ppm. Cumulative exposure over 2 weeks was 13.5 ppm x h. Cell sampling before (2x) and directly after the last exposure and 1, 2 and 3 weeks thereafter. This sampling strategy should enable to capture the optimal time point according to the cell cycle of the oral mucosa. The MN frequencies pre-exposure served as control value. The authors noted that for MN in buccal cell no clear positive control substance has been established. Up to now clearly reproducible effects have not been found in persons with a clearly defined exposure, like for cancer patients under chemotherapy. *Viegas et al. (2010)*: the authors studies 2 groups of workers: anatomy/pathology workers and workers in FA and FA-resin production. It is noted that the MN frequencies in the control group were very low. The exposure situations were for both groups given as 7 h/d and (most probably) 5 d/week. The mean exposures were factory: 0.21 ppm leading to a 2-week cumulative exposure of 14.7 ppm x h laboratory: 0.28 ppm leading to a 2-week cumulative exposure of 19.6 ppm x h. *Ladeira et al. (2011)*: investigation on buccal cells in workers from histopathology laboratories. Although the authors state that MN determination followed the CBMN method (cytokinesis-block micronucleus) this procedure cannot be applied to measure MN in buccal cells. Most probably there was a substantial overlap of subjects studied by Ladeira with those of the study of Viegas et al. (2010). In both of the studies the same number of control subjects was used and the exposure levels were quite similar. Ladeira reported in 85 control subjects a frequency of 0.81‰ MN, but Viegas a very low value of 0.13‰. Interestingly in the study of Viegas the MN frequencies of the exposed pathology/anatomy workers (0.64‰) are slightly below and those of the factory workers (1.27‰) only slightly above the control value of the Ladeira study (0.81‰). This discrepancy between two studies of essentially the same group of investigators questions the reproducibility of the measurements. The foregoing study of Viegas et al. (2010) is not mentioned in the Lareida publication although many of the authors are involved in both studies. For calculation of the 2-week cumulative exposure the same exposure situations are taken as for the Viegas study: 7 h/d, 5 d/week. With a mean	approach using expert judgment has to be applied." The proposed classification Muta 2 for formaldehyde is therefore fully relevant. On section 5.b, both studies Dallas 1992 and Neuss 2010c are performed based on non standard test protocol, which are not available for lung lavage cells. In these assays, the difference in the number of cells analysed comes from the type of endpoint analysed (chromosomal aberration vs Comet). Besides, it is noted that the number of animals investigated in both studies were similar (5 vs 6, respectively), which limits the difference in sensitivity for both assays. Finally, the	

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		TWA of 0.16 ppm a cumulative exposure of 11.2 ppm x h is obtained. *Zeller et al. (2011)*: investigation on nasal cells in volunteers exposed over 5 days (4 h/d) at defined exposures of 0.3-0.7 ppm with peaks up to 0.8 ppm. Cumulative exposure over the 5 days was 8.3 ppm x h. Cell sampling before and directly after last exposure and 1, 2 and 3 weeks thereafter. This sampling strategy should enable to capture the optimal time point according to the cell cycle of the oral mucosa. The MN frequencies pre-exposure served as control value. In addition, the positive studies on local mutagenicity in the upper respiratory tract of exposed humans must also be interpreted in the light of a recent animal study. Exposure of rats up to 15 ppm for 4 weeks led as expected to a marked cell proliferation in the nasal tissues, but the rate of MN induction was not increased (Speit et al., 2011). **In conclusion,** there are positive and negative studies for micronuclei in buccal or nasal cells of humans exposed to FA. These data are taken as supportive evidence in the CLH report for the classification of FA as carcinogenic cat 1A as stated on p. 11: "Indication of local genotoxicity in exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal mucosa cells in several studies." Two independent reviews (BfR, 2006; Appel et al., 2006; Speit, Schmid, 2006) have questioned the reliability of the database on local MN induction in workers. In addition, the positive findings in humans are contradicted by an animal study with high, well defined exposures (Speit et al., 2011). The most relevant negative studies are those of Speit et al. (2007a) (buccal cells) and of Zeller et al. (2011) (nasal cells). The number of exposed subjects is the highest in the Zeller study compared to other investigations on nasal cells. As regards buccal cells, the number of subjects in the Speit study compares well to the other studies apart from those of Viegas et al. (2010) and Lareida et al. (2011). Similarly, the peak exposures and the 2 week cumulative exposures of the Zeller and Speit studies are in the same range as the other studies, apart from Burgaz et al. (2001, 2002) and Ye et al. (2005). But these latter studies gave only very crude exposure estimates relying on stationary measurements.	study by Sul 2007 also performed a Comet assay in lung tissues and observed a dose-related increase in DNA damage. In this study, a significant increase in lipid and protein oxidation was also observed in the lung tissues at the highest dose and may be identified as a biomarker for FA effect in this tissue. The indirect evidence given in the comment that FA doesn't reach the lung comes from from a modeling study in human and does not allow to dismiss any potential contact in rat. We agree that the study by Migliore 1989 is not relevant for inhalation exposure situations. However, it is	

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		Overall the negative Speit and Zeller studies are well comparable to the other investigations reporting an increase of MN in nasal and buccal cells with regard to the number of subjects and the exposure situations. An important advantage of the Speit and Zeller studies is the clearly defined exposure situation. Here the highly variable exposure concentrations and possible confounding by other substances at the workplace is excluded. There is good evidence that coexposure to other substances may have played a role from Ballarin et al. (1992) and Norppa et al. (1992) (wood dust) or from Burgaz et al. (2001) (different solvents). It should be noted that some studies showed extremely high (Norppa et al., 1992) or low (Suruda et al., 1993; Viegas et al., 2010; Ladeira et al., 2011) MN frequencies in control samples and this may indicate to problems with scoring in these studies. Finally no dose response relationship was found by Ballarin et al. (1992) and Norppa et al. (1992) although their subgroups differed considerably with regard to the exposure concentrations. This may indicate to co-exposure to an unknown confounding substance. Therefore, a weight of evidence assessment should put the emphasis on the studies of Speit et al. (2007a) and Zeller et al. (2011) carried out under strictly defined conditions. The positive studies on workers can therefore by no means be taken as sufficient evidence for the local mutagenicity of FA on the upper respiratory tract. These studies cannot be used as supportive evidence for a Cat.1 carcinogenicity classification. The findings of mutagenicity in the upper respiratory tract in humans are not supported by an animal study with inhalation exposure up to 15 ppm. **4.d. SUMMARY** According to CLP regulation, section 3.6.2.2.5. there are several factors that "can be viewed as either increasing or decreasing the level of concern for human carcinogenicity."	relevant to detect the potential of FA to induce mutagenicity in somatic cells at the site of contact. All routes of exposure are considered relevant by the CLP criteria for this purpose of classification in category 2. Positive results by intra-peritoneal route also support this classification. On the minor comments related to page 82/83 of the CLH report (page 40 of the comment), the references given in this statement of the CLH report can be misleading and we clarify here that DPX in the respiratory tract were observed only in monkeys (Casanova 1991). The remarks on the level of adducts at lower	

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		In section 3.6.2.2.6. these factors are listed. The criteria a-f, h and I do not provide arguments for a cat.2 classification and the most important criteria to differentiate between cat. 1A and 2 for FA are: g. structural similarity to a substance(s) for which there is good evidence for carcinogenicity l. the possibility of a confounding effect of excessive toxicity at test doses m. mode of action and its relevance to humans, such as *cytotoxicity with growth stimulation*, mitogenesis, immunosuppression, mutagenicity. In vitro FA is clearly genotoxic and mutagenic leading predominantly to DPX formation and chromosome mutations in mammalian cell systems in the range of cytotoxic concentrations. There is evidence for a practical threshold for induction of micronuclei and SCE. FA after having entered a cell of primary contact is not passed on to neighbour cells. After in vivo inhalation exposure exogenous FA leads to DPX formation, DNA adducts and DNA-DNA cross links only in nasal tissue of rats but not in organs remote from the site of first contact. DPX and DNA adduct formation have a highly non-linear dose response relationship. On the other hand, DNA adducts and DNA-DNA cross links have been identified stemming from endogenous FA in all tissues investigated. Mutagenic effects have not been reliably demonstrated locally or systemically after inhalation exposure in experimental animals or humans. FA leads to cytotoxic irritation with increased regenerative cell replication in the nose of exposed rats. A threshold has been demonstrated for the increase of cell replication at =/>2ppm in rats. This has to be seen in the context of efficient metabolic detoxification of FA in all tissues (biological half life of about 1 min); half saturation of the detoxification pathway was estimated to occur at exposure concentrations of 2.6 ppm.	concentration in Lu 2011 has been commented in the revised CLH report. In conclusion, we consider that positive evidence in mutagenicity tests are available from induction of chromosomal aberrations in rats by inhalation at high dose (Dallas 1992) and of micronuclei in rats in the GI tract by oral route (Migliore 1989). These positive data are further supported by in vitro positive results in numerous genotoxicity and mutagenicity tests, in vivo induction of DNA adducts and DPX at the site of contact, indications of consistent increases in micronuclei frequency in	

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		Histopathological lesions are already induced in the nose of rats after a single day of exposure to the carcinogenic concentrations of 10 and 15 ppm. Extensive ulceration is already found after 4 days and squamous metaplasia after 9 days of exposure. Mild effects occur after a few days at 6 ppm. By prolonged exposure such lesions progress to hyperplasia and squamous metaplasia and finally to carcinomas. There is a clear difference in the sensitivity of different species with regard to the carcinogenic activity of FA: mice are much less sensitive than rats and hamsters did not develop respiratory tumors after inhalation exposure. Furthermore, for the induction of cell proliferation and histopathological lesions much higher exposure concentrations are necessary for mice than for rats. There is no reliable experimental or epidemiological evidence or a mechanistic basis for induction of systemic tumors. These data lead to the conclusion that tumor development depends on excessive cytotoxicity leading to increased cell proliferation. Genotoxicity is of minor importance. Without such pronounced cytotoxicity and regenerative cell proliferation no tumors will develop. In addition, a carcinogenic effect of FA is only to be expected by inhalation exposure. The toxicological profiles of FA and acetaldehyde are basically identical, apart from their potency, justifying the same classification for FA as that for acetaldehyde, namely cat. 2 under the CLP regulation. **In conclusion,** apart from differences in species sensitivity, especially three of the criteria mentioned above need to be taken into consideration for a classification decision of FA, namely g. structural similarity to a substance(s) for which there is good evidence for carcinogenicity l. the possibility of a confounding effect of excessive toxicity at test doses m. mode of action and its relevance to humans, such as *cytotoxicity with growth stimulation*, mitogenesis, immunosuppression, mutagenicity.	humans at the site of contact and positive studies by intra-peritoneal route and a classification Muta 2 is warranted.	

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		In humans tumors of the upper respiratory tract may only develop under conditions of high cytotoxicity with prolonged growth stimulation. Under these considerations FA was formerly classified as a category 3 carcinogen. Since that time no additional data have been reported that might call the former classification into question. Therefore these arguments also pertain to the new CLP regulation and would lead to category 2. There are positive and negative studies for micronuclei induction in buccal or nasal cells of humans exposed to FA. These data are taken as supportive evidence in the CLH report for the classification of FA as carcinogenic cat 1A. A weight of evidence assessment showed that the negative studies of Speit et al. (2007a) and Zeller et al. (2011) carried out under strictly defined conditions are the most reliable ones to assess local mutagenicity in the upper respiratory tract of humans. The positive studies on MN induction in workers reported by other authors can by no means be taken as sufficient evidence for such a local mutagenicity. Therefore the overall database on MN induction in nasal or buccal cells in humans cannot be used as supportive evidence for a Cat.1 carcinogenicity classification. In addition the negative studies in humans are supported by an inhalation study in rats not leading to MN formation in the nose at exposures up to 15 ppm. **5. COMMENTS ON THE PROPOSAL TO CLASSIFY FOR MUTAGENICITY CAT. 2** **5.a. Regulatory situation and general comments** Chapter 3.5. of the CLP regulation deals with deals with the classification for mutagenicity. Already in the heading it is made clear that this relates to "Germ cell mutagenicity". In 3.5.1. only the general definitions for mutation and genotoxicity are given and 3.5.2. relates to the classification criteria. According to 3.5.2.1. "This hazard class is primarily concerned with substances that may cause mutations **in the germ cells** (emphasis added) of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ		

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		cells in vivo are also considered in classifying substances and mixtures within this hazard class." The second sentence means that in vitro test results or somatic cell data have also to be considered with respect to the potential that a substance may cause **germ cell mutations**. The primary concern for germ cell mutagenicity if further underlined by 5.5.2.2. "For the purpose of classification for **germ cell mutagenicity**…" and specifically also in the criteria for category 2: "Substances which cause concern for humans owing to the possibility that they may induce **heritable mutations in the germ cells** of humans (emphasis added)." It goes on that "The classification in Category 2 is based on: — positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: — somatic cell mutagenicity tests in vivo, in mammals; or — other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays." But this evidence clearly must be in line with the primary concern for germ cell mutagenicity. Section 3.5.2.3. defines "Specific considerations for classification of substances as **germ cell mutagens"** and again this heading shows that this classification is related to **possible effects on germ cells**. In 3.5.2.3.1. test system to be considered are mentioned but the following parts make again clear that this relates to germ cells: 3.5.2.3.2. "The system is hazard based, classifying substances on the basis of their intrinsic ability to **induce mutations in germ cells** (emphasis added)." 3.5.2.3.3. "Classification for heritable effects in human **germ cells** is made on the basis of well conducted, sufficiently validated tests …(emphasis added)". These criteria for germ cell mutagenicity have to be applied to FA taking into account that by its intrinsic high reactivity FA will only act on tissues of primary contact. The lack of systemic effects has been shown after long term inhalation and oral exposure and it has been substantiated by the most recent mechanistic studies: after inhalation exposure to labeled FA no increase of DNA adducts in tissues not at the site of first contact and no increase of the blood concentration stemming from the exogenous FA were found (the references		

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		are given in the sections above). Therefore, as FA does not reach distant targets apart from the site of first contact, germ cell effects (in the sense of mutagenicity or genotoxicity) after inhalation, oral or dermal exposure can be excluded and the basic criteria and the definition of germ cell mutagenicity are not met. The restriction to germ cell mutagenicity is also valid when interpreting the "guidance document for CLP". In the section on "Classification as a Category 2 mutagen" it is stated: „A Category 2 mutagen classification may also be based on positive results of a least one *in vivo* valid mammalian genotoxicity test, supported by positive *in vitro* mutagenicity results (p. 186)." This might be interpreted as pertaining to FA as its local genotoxicity has been demonstrated (e.g. DNA adduct formation at the site of first contact) as well as its in vitro mutagenicity, especially MN formation. But nevertheless it is made clear in the flow diagram, that such effects must be interpreted in the light of germ cell effects (p. 189): "**According to the criteria, does the substance cause concern for humans owing to the possibility that it may induce** (emphasis added) heritable mutations in the germ cells of humans?" **5.b. Comments on specific studies** Although the toxicological profile does not warrant a classification for mutagenicity, in the following we want to comment on specific arguments given in the CLH report to support mutagenicity classification. These arguments are summarized on p.10, last paragraph: "On mutagenicity, positive evidence are available i*n vivo* at the site of contact in somatic cells. They consist in induction of chromosomal aberrations in rats by inhalation at high dose (Dallas 1992) ….." Regarding the Dallas study, further details are given on p. 82/83: "Besides, weak but positive genotoxic effects are observed such as the induction … of chromosomal aberrations in pulmonary cells at the highest dose of 15 ppm by inhalation (Dallas 1992). Compared to the OECD guideline, this latter study display no positive control and fewer cells were analysed than recommended (50 cells/animal instead of 100 in the guideline). However, these limitations were not considered to affect the validity of the study considering that a positive and statistically significant effect was observed at the highest dose in spite of the small number of cells analysed. … The recent study by Neuss *et al.*		

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		(2010a) also found no evidence of DPX in the modified Comet assay and did not reproduce the induction of chromosomal aberrations in its micronucleus assay under experimental conditions comparable to Dallas *et al.* (1992). It should be noted that in Neuss 2010a the positive controls did not give an appropriate response for micronuclei induction. This study was performed according to a non-standard protocol that may explain why the standard positive control used in this assay is not appropriate in this case." If the Dallas study is to be used as an argument for mutagenicity classification, it must be critically evaluated against the most recent negative study of Neuss (2010a). It is not sufficient to say that in the Neuss study "the positive controls did not give an appropriate response", as Dallas did not try a positive control substance at all, or that the Neuss study "was performed according to a non-standard protocol" as the same argument applies to Dallas and there is no standard protocol available for MN induction in lung lavage cells. So both studies have to be assessed on their own merits. Notwithstanding that both were "non-standard protocol" studies, in contrast to Dallas, the Neuss study was carried out under GLP conditions so that every finding can be verified. One important point is the sensitivity and statistical reliability of both studies: the finding of Dallas rely on 50 cells each from 5 animals per group being scored (in total 250 cells) while Neuss investigated 2000 cell each from 6 animals per group (in total 12000 cells). Thus a chance finding in the Dallas study cannot be excluded when comparing the diverging findings of both investigations. In addition, in the Neuss study the lavage cells were investigated by the standard Comet assay (for DNA strand breaks and alkali-labile sites) as well as in a modified version with gamma irradiation (for DPX formation). For this part of the study MMS was used as positive control substance and led to the expected effect in the lavage cells. In contrast, no FA related effects were found in both of these comet assays, especially there was no increase in DPX, this lesion being the precursor of cytogenetic effects. This endpoint is not covered by Dallas. One important point that sheds serious doubt whether the Dallas study was done according to nowadays state of the art can be derived from the discussion in the Neuss publication. Obviously the investigation published as Dallas et al. (1992) was already carried out in 1983 and reported as an abstract in 1985 (Scott et al., 1985). Only later in 1988 the rodent lung-macrophage chromosome assay was established in mice and Chinese hamsters. Thereby baseline aberration frequencies for mice of 1.2% and for hamsters of 0.75%		

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		were established. Another study is referenced by Neuss with a control aberration frequency in rats of 1%. The reason for the high control aberration frequencies of the Dallas study remains unknown, but is not in line with other more recent publications. Dallas et al. themselves are very cautious in the interpretation of their results stating "however, the iological significance of this finding is uncertain. This is because the chromosome damage was marginal, it only occurred at a dose that is carcinogenic to the nasal cavities of rats, and there is no evidence that this dose of formaldehyde is carcinogenic to the lung of rats." At exposure concentrations of up to 15 ppm over 2 years no lung lesions were reported, but histopathological changes were confined to the nasal cavity and the proximal trachea (Kerns et al., 1983; Sellakumar et al., 1985). That FA does not reach the lung of rats was later indirectly confirmed by modeling the FA flux into the pulmonary regions of humans (Overton et al., 2001). Under the condition of rest that is comparable to the situation of rats in inhalation experiments, the FA flux virtually becomes zero in the region of the 10th bronchial generation (division of the conducting airways) and no FA will reach the pulmonary region beyond the terminal bronchioles. In addition it has to be taken into account that the rat nose more efficiently extracts FA from inhaled air as compared to that of primates: while FA at 6 ppm induced histopathological lesions in the trachea and bronchial bifurcation of monkeys (Monticello et al., 1989), such effects were not noted in rats at 5.6 ppm after chronic exposure (Kerns et al., 1983). And even in monkeys no DPX (Heck et al., 1989) or histopathological lesions (Monticello et al., 1989) were found in the proximal lung. In addition it is stated on p.10, last paragraph: "On mutagenicity, positive evidence are available i*n vivo* at the site of contact in somatic cells. They consist in induction ….. of micronuclei in rats in the gastrointestinal tract by oral route (Migliore 1989)." Regarding the Migliore study, it is stated on p. 82: "….weak but positive genotoxic effects are observed such as the induction of respectively micronuclei at irritating doses in the gastrointestinal tract via oral route (Migliore 1989)…..". In this study FA was given orally at a single high dose of 200 mg/kg and MN were analyzed 16, 24 and 39 h after treatment. MN were observed in the stomach and to a lesser extent in duodenum, ileum and colon. The frequency		

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		of MN increased with time after treatment. In addition other nuclear abnormalities indicative for cytotoxicity were observed in parallel to a high extent. It is noted that MN induction was clearly correlated with local irritation: hyperemia and hemorrhage. Maximal effects for MN induction and histopathological signs of severe irritation were both observed at the latest time of sacrifice, indicating that both effects were interrelated to each other. The effects obtained under this very high dose by bolus application can by no means be compared to inhalation exposure situations. Because of the exposure route and the high dose (only one dose level used not allowing to establish a dose response relationship) leading to severe irritation, these results should not be used for a regulatory mutagenicity classification of FA. The classification cat.2 mutagenicity is said to be further supported by (p.10): "These positive data are further supported by *in vitro* positive results in numerous genotoxicity and mutagenicity tests, *in vivo* induction of DNA adducts and DNA-protein crosslinks (DPX) at the site of contact and indications of consistent increases in micronuclei frequency in humans at the site of contact." To our interpretation of the CLP criteria and the corresponding guideline, these data do not support a classification for germ cell mutagenicity. We do not contest "*in vitro* positive results in numerous genotoxicity and mutagenicity tests", nor the ", *in vivo* induction of DNA adducts and DNA-protein crosslinks (DPX) at the site of contact", but the total database shows that these findings will not pertain to germ cells as FA does only act at the site of first contact, not reaching the germ cells by whatever route of exposure. The most recent data in this respect (no systemic DNA adduct or increase in blood concentration after exposure to labeled exogenous FA) have been given above. Finally, the "indications of consistent increases in micronuclei frequency in humans at the site of contact" have also been discussed above in detail. The positive studies from humans at the workplace and the negative studies in volunteers have been assessed in a weight of evidence approach. Thereby we showed that emphasis must be placed on the volunteer studies with exposures under strictly defined conditions. *Minor comments related to p.82/83:* "*In vivo*, at the site of contact, induction of DPX by inhalation was observed in rats in the nasal mucosa and in monkeys in the nasal turbinates and to a lower		

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		extent in the respiratory tract (Casanova 1991, Lu 2010, Lu 2011, Moeller 2011)." Lu et al. (2011) and Moeller et al. (2011) only measured DNA adducts and Lu et al. (2010) determined in addition DNA-DNA adducts but not DPX. The formation of DPX in the respiratory tract (apart from the nose) was found in monkeys but not in rats. "Besides, recent studies able to discriminate between DNA-adducts of endogenous or exogenous origin shows that the level of exogenous DNA-adducts in rat nasal epithelium is of similar order of magnitude than endogenous DNA-adduct level up to 9 ppm but is dramatically increased at 15 ppm (Lu 2011)." If the dramatic increase at 15 ppm is mentioned, it should also be stated, that the increase of adducts by exogenous FA at 0.7ppm amounted to about 1% of endogenous adducts and at 2 ppm to about 3%, clearly within the standard deviation of the endogenous adducts and is by no means "of similar order of magnitude than endogenous DNA-adduct level". Only at 5.8 ppm the increase of 20% reached just the standard deviation of the endogenous adducts (Lu et al., 2011, 2011a). Finally it is mentioned that "DPX were found in the liver cells of mice from 0.8 ppm (Zhao 2009). Im *et al.* (2006) observed DNA damage in the Comet assay in the liver and lymphocytes from 5 ppm." As these studies are obviously not taken as support for mutagenicity cat. 2 classification, they will only briefly assessed here. The results of both of these studies are in conflict with the most recent studies showing that exogenous FA will neither lead to an increase of blood levels nor to DNA adducts or DNA-DNA cross links apart from the site of direct contact. As regards specifically the findings of Im et al. (2006), Speit (2006) pointed in addition to the fact that even if FA had acted systemically the results observed in the comet assay are not biologically plausible. FA leads primarily to DPX formation and DPX reduce DNA migration in the comet assay and do not lead to an increase as reported by Im. **5.c. Summary** Classification for the different mutagenicity categories always refer to germ cell mutagenicity. Due to the high reactivity of FA, DPX, DNA adducts and DNA-DNA cross links have only been observed in the nasal tissue of rats after inhalation. Furthermore, inhalation of FA does not lead to an increase of its		

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		blood concentration. Therefore after exposure by the inhalation, oral or dermal route, FA will not reach the germ cells and a classification for (germ cell) mutagenicity is not warranted. In the CLH report two studies are specifically mentioned as giving support to a mutagenicity cat. 2 classification: Dallas et al. (1992) claimed that chromosomal aberrations in lung lavage cells are induced after inhalation exposure. But this finding could not be reproduced in a recent inhalation study in which neither MN nor DNA strand breaks, alkali-labile sites or DPX were induced in lung lavage cells. This study carried out according to today's standards must be given precedence over the Dallas study. In addition, inhalation studies and mathematical modeling have shown the FA by inhalation will not reach the lung. Migliore et al. (1989) reported MN formation in the gastric mucosa after oral application at a highly cytotoxic dose level leading to hyperemia and hemorrhage. This study can by no means be compared to the inhalation exposure situation. In conclusion there is no reason to classify FA as a cat. 2 mutagen. *End of mutagenicity comment from attachment no. 12 'Scientific response to French CLH report on formaldehdye.pdf' , page 21-41.*		

Toxicity to reproduction

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment

15/12/2011	Portugal/ APEQ-Portuguese Chemicals Association	Please see the Zip file Scientific response to French CLH report formaldehyde.pdf, all over this response. *ECHA Comment: the document 'FORMALDEHYDE RESPONSE.zip' was submitted as a separate attachment. Attachment No.12.*	No comment in this document relates to reproductive toxicity. Besides, reproductive toxicity of formaldehyde is not addressed in the current classification proposal that focus on mutagenicity and carcinogenicity.	Noted.

Respiratory sensitisation

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
21/11/2011	Belgium/ European Trade Union Confederation	Formaldehyde is included in the Trade Union Priority List for REACH authorisation (http://www.etuc.org/a/6023)as a respiratory sensitiser.	The information is noted. However, sensitising properties of formaldehyde are not addressed in the current classification proposal that focus on mutagenicity and carcinogenicity.	Noted.
15/12/2011	Portugal/ APEQ-Portuguese Chemicals Association	Please see the Zip file Scientific response to French CLH report formaldehyde.pdf, all over this response. *ECHA Comment: the document 'FORMALDEHYDE RESPONSE.zip' was submitted as a separate attachment. Attachment No.12. Page 3-7 is copied below.* **1. SUMMARY** Formaldehyde has a very strong epidemiological database (in total about 50000 workers in 3 large cohort studies) and therefore the decision regarding cat. 1A should solely be based on the epidemiology data. In epidemiology based reviews of FA, there appears to be a trend that too much weight is placed on a single group within the National Cancer Institute (NCI) cohort, despite the fact that even the CLH report admittedly states that "the existence of a grouping of cases in plant 1 of the National Cancer Institute (NCI) cohort raises a doubt on potential cofounder and	It is noted that this comment does not refer to respiratory sensitisation but to carcinogenicity and consists in a summary of comments detailed above in the carcinogenicity section. Please refer to this section for response to comments.	See above.

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		lowers the level of evidence". Because of this limitation, the CLH report relies on further arguments as supportive evidence. The supportive arguments are either discussed in the sections related to cat. 1A and cat. 1B classification or in the introduction. Overall, we conclude that the former classification (cat. 2, CLP or cat. 3 DSD) should be maintained. Apart from a discussion on carcinogenicity classification, two further sections deal with classification for mutagenicity and route specific classification. Classification for carcinogenicity cat. 1A: we present data showing that - no consistent evidence can be obtained from the NCI cohort. All risk estimates are driven by plant 1 and cannot be generalized as shown by an interaction analysis. - the grouping of cases in plant 1 cannot be explained by the largest number of subjects being exposed to highest peak exposures. The number of workers with highest peak exposure was larger for all other plants, but the NPC incidence was clearly lower. - the correlation of NPC with peak exposure is rather speculative. A sensitivity analysis showed that the low p-value of 0.02 was possibly distorted downward by the small sample size (only 10 NPCs). Further many NPCs might be related to exposures prior to entering plant 1. And finally the Hauptmann study is incomplete because of 1000 "missing deaths". This can only be clarified by the still missing NCI update. - the case control studies can hardly be used as supportive evidence as demonstrated by a recent metaanalysis. Altogether, the data do not support a causal relationship between formaldehyde exposure and induction of NPC, and do not correspond to a sufficient evidence of carcinogenicity in humans as required for a cat. 1A classification. The most relevant cohort study is not reliable and its update might lead to a significant reevaluation of the relationship between formaldehyde exposure and NPC.		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		Classification for carcinogenicity cat. 1B: According to section 3.6.2.2.5. there are several factors that "can be viewed as either increasing or decreasing the level of concern for human carcinogenicity." In section 3.6.2.2.6. these factors are listed. The criteria a-f, h and i do not provide arguments for a carcinogenicity cat.2 classification and the most important criteria to differentiate between cat. 1A and 2 for FA are: g. structural similarity to a substance(s) for which there is good evidence for carcinogenicity j. the possibility of a confounding effect of excessive toxicity at test doses k. mode of action and its relevance to humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity. FA leads to cytotoxic irritation with increased regenerative cell replication in the nose of exposed rats. A threshold has been demonstrated for the increase of cell replication at =/>2ppm in rats. This has to be seen in the context of efficient metabolic detoxification of FA in all tissues (biological half life of about 1 min); half saturation of the detoxification pathway was estimated to occur at exposure concentrations of 2.6 ppm. Histopathological lesions are already induced in the nose of rats after a single day of exposure to the carcinogenic concentrations of 10 and 15 ppm. Extensive ulceration is already found after 4 days and squamous metaplasia after 9 days of exposure. Mild effects occur after a few days at 6 ppm. By prolonged exposure such lesions progress to hyperplasia and squamous metaplasia and finally to carcinomas. There is a clear difference in the sensitivity of different species with regard to the carcinogenic activity of FA: mice are much less sensitive than rats and hamsters did not develop respiratory tumors after inhalation exposure. There is no reliable experimental or epidemiological evidence or a mechanistic basis for induction of systemic tumors. These data lead to the conclusion that tumor development depends on excessive cytotoxicity leading to increased cell proliferation. Genotoxicity is		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		of minor importance. Without such pronounced cytotoxicity and regenerative cell proliferation no tumors will develop. In addition, a carcinogenic effect of FA is only to be expected by inhalation exposure. The toxicological profiles of FA and acetaldehyde are basically identical, apart from their potency, justifying the same classification for FA as that for acetaldehyde, namely cat. 2 under the CLP regulation. In conclusion, apart from differences in species sensitivity, especially three of the criteria mentioned above need to be taken into consideration for a classification decision of FA leading to cat.2, namely g. structural similarity to a substance(s) for which there is good evidence for carcinogenicity j. the possibility of a confounding effect of excessive toxicity at test doses k. mode of action and its relevance to humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity. In humans, tumors of the upper respiratory tract may only develop under conditions of high cytotoxicity with prolonged growth stimulation. Under these considerations FA was formerly classified as a category 3 carcinogen. Since that time no additional data have been reported that might call the former classification into question. Therefore, these arguments would still also lead to a classification of category 2 under the new CLP regulation. There are positive and negative studies for micronuclei induction in buccal or nasal cells of humans exposed to FA. These data are taken as supportive evidence in the CLH report for the classification of FA as carcinogenic cat 1A. A weight of evidence assessment showed that the negative studies of Speit et al. (2007a) and Zeller et al. (2011) carried out under strictly defined conditions are most reliable to assess local mutagenicity in the upper respiratory tract of humans. The positive studies on MN induction in workers reported by other authors can by no means be taken as sufficient evidence for such a local mutagenicity. These studies are contradicted by animal data, the methods applied are not standardized, it is unlikely that FA may reach the dividing basal cell layers due to the histological structures of the underlying tissues, there are		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		indications for confounding co-exposures, and in some studies the control MN frequencies point to problems with the scoring procedures. In addition the negative studies in humans are consistent with an inhalation study in rats not leading to MN formation in the nose at exposures up to 15 ppm. Therefore the overall database on MN induction in nasal or buccal cells in humans cannot be used as supportive evidence for a Cat.1 carcinogenicity classification. *Classification for mutagenicity cat. 2:* Classification for the different mutagenicity categories always refer to germ cell mutagenicity. Due to the high reactivity of FA, DPX, DNA adducts and DNA-DNA cross links have only been observed in the nasal tissue of rats after inhalation. Furthermore, inhalation of FA does not lead to an increase of its blood concentration. Therefore after exposure by the inhalation, oral or dermal route, FA will not reach the germ cells and a classification for (germ cell) mutagenicity is not warranted. In the CLH report two studies are specifically mentioned as giving support to a mutagenicity cat. 2 classification: Dallas et al. (1992) claimed that chromosomal aberrations in lung lavage cells are induced after inhalation exposure. But this finding could not be reproduced in a recent inhalation study in which neither MN nor DNA strand breaks, alkali-labile sites or DPX were induced in lung lavage cells. This study, carried out according to today's standards, must be given precedence over the Dallas study. In addition, inhalation studies and mathematical modeling have shown that FA by inhalation will not reach the lung. Migliore et al. (1989) reported MN formation in the gastric mucosa after oral application at a highly cytotoxic dose level leading to hyperemia and hemorrhage. This study can by no means be compared to the inhalation exposure situation. In conclusion there is no reason to classify FA as a cat. 2 mutagen. *Route specific classification:* It is proposed that a classification of FA should be limited to the inhalation route. A carcinogenicity classification of FA after oral exposure is not warranted for the following reasons:		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		- No tumors were observed in a guideline 2-year carcinogenicity bioassay - Indications for the development of forestomach papillomas in another study are uncertain due to the unclear histopathological criteria applied - No indications for tumor development were obtained after oral application of two other highly reactive aldehydes. Similarly a classification for the dermal route is not warranted: In experiments with skin application FA did not act as initiator or promotor. Although treatments with FA alone were included in these experiment, a definite answer as to whether FA may be a complete skin carcinogen is not possible by these data. But as FA will only act on cells of its primary contact and taking into account the multilayered structure of the skin, a local carcinogenic activity can be excluded. *End of page 3-7 from attachment no. 12*		
20/12/2011	France/ Women in Europe for a Common Future	*ECHA Comment: Due to technical problem after ECHA launched new web site on 15 December 2011, the'Give Comments' link was active and this comment was received.* *Attachment no. 14 'WECF formaldehyde consultation.pdf' has the same content.* conclusions page 21: WHO identified formaldehyde as a priority indoor air pollutant, producing guidelines on formaldehyde in a document entitled "WHO guidelines for indoor air quality – Selected Pollutants", 2010 source: http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf	The information is noted. However, sensitising properties of formaldehyde are not addressed in the current classification proposal that focus on mutagenicity and carcinogenicity.	Noted.
21/12/2011	Belgium/ Individual	*ECHA Comment: Due to technical problem after ECHA launched new web site on 15 December 2011, the'Give Comments' link was active and this comment was received.* The following well-performed, independent & published, medium-sized study found formaldehyde asthma symptoms in rodents at doses some 600 times lower that the L or NOAEL used for its inhalation DNEL (cancer endpoint, I believe) in its REACh Registration; so perhaps you need to C&L	The information is noted. However, sensitising properties of formaldehyde are not addressed in the current classification proposal that focus on mutagenicity and	Noted.

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		it as even more dangerous than you propose! Irritant and adjuvant effects of gaseous formaldehyde on the ovalbumin-induced hyperresponsiveness and inflammation in a rat model http://informahealthcare.com/doi/abs/10.3109/08958370902806159 Inhalation Toxicology December 2009, Vol. 21, No. 14 , Pages 1200-1207 (doi:10.3109/08958370902806159) Y. Qiao1, B. Li1, G. Yang1, H. Yao1, J. Yang1, D. Liu1, Y. Yan1,2, T. Sigsgaard3, X. Yang1 1College of Life Science, Central China Normal University, Wuhan, China 2School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore, Singapore 3Aarhus University, Institute of Public Health, Environmental and Occupational Medicine, Aarhus, Denmark Prof. Address for Correspondence: Torben Sigsgaard, Aarhus University, Institute of Public Health, Environmental and Occupational Medicine, DK-8000 Aarhus C, Denmark. E-mail: sigsgaard@dadlnet.dk Background: Formaldehyde (FA) is a common indoor air pollutant that can cause asthma in people experiencing long-term exposure. While FA and other man-made chemicals contribute to the stimulation of asthma in the general population, the underlying molecular pathogenesis of this relationship is not yet well understood. Objective: To explore FA as an irritant for the onset of asthma and as an adjuvant for the induction of allergy. Methods: In the present study, 40 Wistar rats in five experimental groups were exposed to: (i) saline; (ii) ovalbumin (OVA); (iii) OVA + FA at 417 ppb; (iv) OVA + FA at 2500 ppb; and (v) FA at 2500 ppb. Current and prior occupational exposure limits in China were established at 417 ppb and 2500 ppb, respectively. Gaseous FA was administrated to the animals for 6 h/day before and during OVA immunization or saline treatment. Measured outcomes included in situ lung function analysis, cytokine measurement, and histological changes in the rat lungs. Results: The airway reactivity, lung histological changes, pulmonary interleukin-4 secretion, and eosinophil infiltration in the OVA and FA	carcinogenicity.	

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		exposed rats were significantly higher after gaseous FA exposures of 417 and 2500 ppb. While FA exposure alone did not induce significant structural changes to the airway, and the rate of inflammatory cell infiltration was the same as for the control group, pulmonary levels of interferon-γ were significantly elevated in the exposed rats. Conclusions: FA may be an irritant as well as serve as an adjuvant for the onset of asthma or asthma-like symptoms.		

Other hazards and endpoints

Date	Country/ Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
09/11/ 2011	United Kingdom / Daen Color UK Ltd.	Threshold for Hazardous Preparation Classification should be stated.	This information is out of the scope of the classification discussion. For information, in absence of proposed specific concentration limits the proposed classifications Muta 2 applies at concentrations ≥ 1.0% and Carc 1A at concentrations ≥ 0.1%.	No further comment.
12/12/ 2011	Germany/ Plog/ MSCA	See attached document *ECHA Comment: The attachment 'DE-MSCA_Comment on Formaldehyde.doc' Specific comments: Toxicokinetics is copied below. Attachment No.3* **Specific comments:** **Toxicokinetics:** <u>General:</u> The following information regarding differences in deposition in the respiratory tract between rats and humans may be	The difference in deposition in the respiratory tract in rats and humans is	Agreed.

Date	Country/ Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		useful when discussing effects *in vivo* and correlating effects in rats and humans: Generally, the site of deposition and absorption is dependent on species specificities in nasopharyngeal anatomy, mucous clearance and breathing pattern. Mathematical modelling has predicted ~ 90 and ~ 70 % (± 14 %) of absorption of formaldehyde gas already within the nasal passages in rats and primates, respectively, at rest (Kimbell et al., 2001a)[8]. With increasing activity and oronasal breathing, however, larger fractions (~ 45 %) are predicted to be absorbed in the tracheobronchial region in man, while deposition in the pulmonary region is modelled to be more than 1000-fold lower than in the airways (Kimbell et al., 2001b[9], Overton et al., 2001[10], BfR, 2006). <u>Page 19, 3rd paragraph, Section 4.1:</u> In addition to metabolic incorporation of formaldehyde, distributed radioactivity may also result from other metabolic products such as formiate (esp. in kidneys) and reactions products /adducts (rf. to comment below). <u>Page 19, 3rd paragraph, Section 4.1:</u> Further potential pathways should be considered in the context of epidemiological evidence for lymphohaematopoetic cancer: In addition to formic acid, adducts of formaldehyde with urea (N-hydroxymethylurea, N,N'-bis-(hydroxymethyl)urea, polymethyleneurea) were identified as the major urinary metabolites in rats, accounting for 20-45 % of urinary radioactivity in the study by Mashford and Jones (1982)[11] (formic acid: 55-80 %). It was further suggested, that the urinary metabolite thiazolidine-4-carboxylate identified in exposed Wistar rats was formed *in situ* by chemical reaction of excreted cysteine with formaldehyde released from an unidentified unstable adduct such as hydroxymethylurea. Primary adducts with DNA include N6-	discussed in section 4.10.5. (p 172) when discussing potential species specificities. The differences described in this comment supports that tumours are observed in the nasal cavity in rats and in lower parts of the respiratory tract in humans. In rats exposed by inhalation to either 0.63 or 13.1 ppm of [^{14}C]-formaldehyde for 6 h, about 40% of the inhaled ^{14}C was exhaled in the expired air as [^{14}C]O_2 during the 70 h post-exposure period, 17% was excreted in the urine, 5% was eliminated in the faeces, and 35-39% remained in the tissues and carcass (Heck 1983). Casanova-Schmitz (1984) showed that radioactivity in the tissue and in particular in bone marrow was not due to covalent adducts to	Noted. Noted, evidence for systemic carcinogenic effects was considered insufficient.

[8] Kimbell JS, Subramaniam RP, Gross EA, Schlosser PM, Morgan KT, 2001a, Dosimetry modeling of inhaled formaldehyde: comparisons of local flux predictions in the rat, monkey, and human nasal passages. Toxicol Sci 64(1):100-10.

[9] Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB, Miller FJ, 2001b, Dosimetry modeling of inhaled formaldehyde: binning nasal flux predictions for quantitative risk assessment. Toxicol Sci 64(1):111-21

[10] Overton, J. H.; Kimbell, J. S.; Miller, F. J. 2001, Dosimetry Modeling of Inhaled Formaldehyde: The Human Respiratory Tract. Toxicol. Sci. 64 (1): 122-134.

[11] Mashford PM, Jones AR. 1982, Formaldehyde metabolism by the rat: a re-appraisal. Xenobiotica. 12(2):119-24.

Date	Country/ Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
		hydroxymethyldeoxyadenosine (hm6dA), hm4dC, hm2dG and hm3dT. These are reported to become unstable when DNA is hydrolysed, releasing formaldehyde, but to be sufficiently stable in genomic DNA to react with proteins into cross-linked products (Casanova et al., 1989). Similar formaldehyde adduct formation has been reported for RNA and proteins (Casanova and Heck, 1987)[12]. The product of the reaction of formaldehyde with the N-terminal valine of albumin in rats and humans has been proposed as a biomarker for formaldehyde exposure (Bono et al., 2006[13]; Li et al., 2007[14]). <u>Page 20, 2nd paragraph:</u> The method for measurement of formaldehyde in blood was based on acidic derivatisation with pentafluorophenylhydrazine (PFPH method) or chromotropic acid which detects free formaldehyde as well as many of its adducts/conjugates including those with tetrahydrofolate or glutathione and other (unidentified) formaldehyde species (Heck et al., 1982). It is thus not capable of detecting a potential difference in the pattern of "*formaldehyde species*" or the arrival of any new relevant species. The value of this analysis is further limited by the ratio of background signal and expected contribution from inhalation exposure. Thus, the evidence from these studies should not be regarded sufficient to dismiss epidemiologic indications for an association with systemic cancer. *End of attachment no. 3 – Specific comments: Toxicokinetics*	macromolecules but to metabolic incorporation. It is however not in contradiction with the identification of urinary formaldehyde metabolites and adducts. It is also noted that the study by Mashford (1982) seems to be performed by intra-peritoneal or oral route. It is also noted that DNA adducts to formaldehyde has been identified *in vitro* (Lu 2009). In vivo by inhalation, they also have been detected at the site of contact in rats (Lu 2010 and 2011) and in macaque (Moeller 2011) but not at distant sites such as blood, spleen, thymus, liver, bone marrow and liver in rats up to 10 ppm, 6hr/d for 5 days (Lu 2010), in bone marrow in rats up to 15 ppm for 6 hr (Lu 2011) or in bone marrow in macaque up to 6 ppm, 6hr/d for 2 days.	
14/12/	Belgium/	See attached report, p41-45	It is recognised that the	Please note the

[12] Casanova M, Heck H. 1987, Further studies on the metabolic incorporation and covalent binding of inhaled 3H- and 14C-formaldehyde in Fischer-344 rats: effect of glutathione. Toxicol Appl Pharmacol, 89: 105-121

[13] Bono R, Vincenti M, Schiliro' T, Scursatone E, Pignata C, Gilli G. 2006, N-Methylenvaline in a group of subjects occupationally exposed to formaldehyde, Toxicol Lett., 161(1):10-7

[14] Li H, Wang J, König R, Ansari GA, Khan MF. 2007, Formaldehyde-protein conjugate-specific antibodies in rats exposed to formaldehyde. J Toxicol Environ Health A, 70(13):1071-5

Date	Country/ Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
2011	Formacre	Additional comment on route specific classification Classification of FA should be limited to the inhalation route. A carcinogenicity classification of FA after oral exposure is not warranted for the following reasons: - No tumors were observed in a guideline 2-year carcinogenicity bioassay - Indications for the development of forestomach papillomas in another study are uncertain due to the unclear histopathological criteria applied - No indications for tumor development were obtained after oral application of two other highly reactive aldehydes. Similarly a classification for the dermal route is not warranted: In experiments with skin application FA did not act as initiator or promotor, but by these studies a definite answer as to whether FA may be a complete skin carcinogen may not be possible. But as FA will only act on cells of its primary contact and taking into account the multilayered structure of the skin, a local carcinogenic activity can be excluded. *ECHA Comment: The document: 'formacare submission.zip' was submitted as a separate attachment. Attachment No.6. which is the same document submitted from Portugal/Lubelia Penedo/APEQ-Protuguese Chemicals Association (attachment no. 12 file name 'Scientific response to French CLH report on formaldehdye.pdf')*	proposed carcinogenic classification is entirely based on data obtained by the inhalation route either in humans or in experimental animals. The route of exposure can be specified in the hazard statement "if it is conclusively proven that no other routes of exposure cause the hazard". In particular for the dermal route reliable carcinogenicity studies are not available in experimental animals. It is recognized that due to its reactivity formaldehyde is expected to form adducts at the site of contact by dermal route that limits the absorption throughout the skin layers. However, an *in vitro* study performed with [14C]formaldehyde has shown that some radioactivity is measured in the diffusion cell (see toxicokinetics section of the CLH report). Although it is not known whether radioactivity is present as formaldehyde, metabolite or adduct, a potential contact of formaldehyde or its metabolites with the deeper layers of the skin	respective part in the opinion document. Data on other routes than inhalation are not sufficient to exclude a carcinogenic potential. Thus limiting the classification to the inhalation route can not be justified.

Date	Country/ Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
			cannot be excluded. The present database therefore does not allow proving that formaldehyde does not have a carcinogenic effect by dermal route and it is proposed not to specify the route of exposure in the hazard statement.	
15/12/ 2011	Denmark/ MSCA	Repeated dose toxicity Although not proposed a further classification with STOT RE 1 which repect to the respiratory tract as the target organ in connecting with inhalational exposure should be considered as well. The available animal data in the CLH report supports such a classification as epithelial cell hyperplasia, epithelial dysplasia, and squamous cell metaplasia in the nasal mucosa have been observed in several rat inhalation studies at levels of 2 and 5.6 ppm (2.5 and 6.9 mg/m3); in mice at 6.7 and 17.2 mg/m3, and in hamster at 12 mg/m3 (see tables 17 & 25 in the CLH report). This is far below the guidance value of 200 mg/m3 for STOT RE 1 classification. The relevance of this classification is further supported by human data as described in the IARC (2006) evaluation under the section regarding ´Effects of chronic exposure on nasal mucosa´; ´occupational exposure´.	The comment is noted. However, repeated dose toxicity properties of formaldehyde are not addressed in the current classification proposal that focus on mutagenicity and carcinogenicity	Noted.
15/12/ 2011	United Kingdom/ MSCA	Inclusion of STOT SE 3-H335 to the overall classification may be superfluous as classification as corrosive would implicitly cover corrosion/irritation of the respiratory tract. Our understanding is that inclusion of a SCL for STOT SE3-H335 is required to warn of possible respiratory tract irritation in mixtures employing sub-corrosive concentrations of formaldehyde.	We agree that corrosive classification implicitly cover corrosion/irritation. However, when formaldehyde is present in a mixture at a concentration triggering a classification as irritant, only application of skin and eye irritant classifications is foreseen by CLP. An	There is no focus on this endpoint in the CLH dossier.

Date	Country/ Organisation / MSCA	Comment	Dossier submitter's response to comment	The RAC's response to comment
			additional classification STOT SE 3 for respiratory irritation may therefore be relevant. It would also be consistent with additional classification R37 according to the DSD.	
15/12/ 2011	Portugal/ APEQ- Portuguese Chemicals Association	Please see the Zip file Scientific response to French CLH report formaldehyde.pdf, all over this response. *ECHA Comment: the document 'FORMALDEHYDE RESPONSE.zip' was submitted as a separate attachment. Attachment No.12*	It is noted that this comment does not refer to any other endpoints but to carcinogenicity and mutagenicity. Please refer to the section related to these two endpoints for response to comments.	No comment.

ATTACHMENTS RECEIVED*:*

1. **FA_CLH.pdf - Comments on the CLH Report for Formaldehyde.** Submitted by Germany/ Guenter Speit/ Individual. *Comment is copied in the table in Mutagenicity section.*

2. **Texte proposé pour le FORMACARE.doc - Formaldehyde resins harmlessness.** Submitted by Belgium/ Georges Francis/ ADVACHEM. *Comment is copied in the table.*

3. **DE-MSCA_Comment on Formaldehyde.doc - Comments on the CLH-Dossier for Formaldehyde (CAS-No.: 50-00-0) from the FR-CA.** Submitted by Germany/ Matthias Plog/ MSCA. *Comment is copied in the table.*

4. **Formaldehyde_Response_to_ECHA.pdf – Statement of the wood-panels industry concerning the proposal from France to reclassify formaldehyde.** Submitted by Belgium/ Kris Wijnendaele/ European Panel Federation aisbl. *Attachment text is the same in the table*.

5. **ACEA position on Formaldehyde_20111214.pdf – ACEA Comments to the Annex XV dossiers proposing harmonised Classification and Labelling for Formaldehyde.** Submitted by Belgium/ Peter Kunze/ ACEA - European Automobile Manufacturers Association. *Attachment text is the same in the table.*

6. **formacare submission.zip - Response to the Annex XV dossier submission for the harmonised classification and labeling of formaldehyde.** Contains 2 files : **141211 cover letter.pdf** and **Scientific response to French CLH report on formaldehdye.pdf**. Submitted by Belgium/ Phil Hope/ Formacare. *Part of comment is copied in the table.*

7. **FORESA position on formaldehyde reclassification proposal.zip**. Contains 4 files : 1)ASEPEYO Statement for Foresa.pdf, 2) Foresa position.pdf, 3)FREMAP Statement for Foresa.PDF and 4)Medical Statement for Foresa.pdf. Submitted by Spain/ Ester Cabrera/ Foresa, Industrias Químicas del Noroeste, S.A.U. *Attachments are copied in the table.*

8. **BRESFOR position.zip** Contains 2 files : BRESFOR position.pdf and Medical statement BRESFOR.pdf. Submitted by Porugal/ Rui Pereira da Costa/ BRESFOR, Industria do Formol, S.A. *Attachment copied in the table.*

9. **2011_ACC submitted comments ECHA FR dossier.pdf - ACC comments on Annex XV dossier proposing harmonized classification and labeling (CLH) draft report for Formaldehyde, version 2 (28 September 2011)**. Submitted by United States/ Ann Mason/ American Chemistry Council. *Comment is not copied in the table.*

10. **2011_ENVIRON detailed comments on the CLH FR dossier Formaldehyde.pdf.** Submitted by the United Kingdom/ Sue Bullock/ Momentive Specialty Chemicals UK Limited. *The first 2 pages are copied in the table.*

11. **Lonza_Formaldehyde_Comments_111215.doc – Response by Lonza.** Submitted by the United Kingdom/ Jack Poppleton/ Lonza. Attachment copied in the table.

12. **FORMALDEHYDE RESPONSE.zip.** Contains 2 files : APEQ TECHNICAL NOTE 013 2011.pdf (***comment is copied in the table***) and Scientific response to French CLH report on formaldehdye.pdf (***part of comments are copied in the table***). Submitted by Portugal/ Lubelia Penedo/ APEQ-Portuguese Chemicals Association. *Part of comment is copied in the table.* ***Same document as attachment no. 6.***

13. **APEQ Medical Declaration.doc - APEQ ASSOCIATED MEMBERS POSITION.** Submitted by Portugal/ Lbelia Penedo/ APEQ-Portuguese Chemicals Association. *Comment is copied in the table except the embedded document 'Medical CEMETRA Declaration.pdf' in Portuguese.*

14. **WECF formaldehyde consultation.pdf.** Submitted by France / Elisabeth Ruffinengo / Women in Europe for a Common Future. *Attachment text is the same in the table.*

ECHA note: Belgium / Formacare has provided the same document 'CLASSIFICATION LABELING AND PACKAGING OF SUBSTANCES AND MIXTURES – Response to the Annex XV dossier submission for the harmonised classification and labelling of formaldehyde' as Portugal/APEQ-Protuguese Chemicals Association (attachment no. 6 and 12 file name 'Scientific response to French CLH report on formaldehdye.pdf' *)*

Annex I

Number of subjects in the highest peak exposure category and number of NPC deaths by plant of the NCI cohort

	Plant 1	Plant 2	Plant 3	Plant 4	Plant 5	Plant 6	Plant 7	Plant 8	Plant 9	Plant 10
Number of subjects [a,b]	4261	784	2375	1692	744	5248	4228	1679	1933	2675
Number (and %) of subjects in the highest peak category [b]	1964 (46.1%)	718 (91.6%)	0 (0%)	1233 (72.9%)	152 (20.4%)	105 (2%)	169 (0.4%)	18 (1.1%)	180 (9.3%)	1864 (69.7%)
Number of exposed NPC cases [b, c]	6						1			1
Number of exposed cases in the highest peak category [b, c]	6						1			1
Number of unexposed NPC cases [b, c]		1	1							

Source of information:

[a] Hauptmann 2004

[b] Marsh 2005

[c] allocation to exposure categories of NPC deaths in plants 2-10 is based on the information given in the comments submitted during CLH public consultation by ACC (attachment 9 – Comments by GM Marsh).