Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Glutaraldehyde

EC number: 203-856-5
CAS number: 111-30-8

CLH-O-0000004237-75-03/F

Adopted

6 June 2014

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COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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

Substance name: glutaral; glutaraldehyde; 1,5-pentanedial
EC number: 203-856-5
CAS number: 111-30-8
Dossier submitter: Finland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Switzerland	Dow Benelux B.V. and BASF SE	Company-Manufacturer	1

Comment received

The Dow Chemical Company and BASF SE have been involved in a productive relationship with the Finnish Competent Authority throughout the evaluation of glutaraldehyde under the BPD and as such welcomes the opportunity to comment on the CLH dossier of glutaraldehyde.

We agree on the proposed classification/conclusion **with exception of the following points;**

Human Health

1. Acute Tox 1; H330 for inhalation
2. Skin Sens 1A H317 with a proposed SCL (specific concentration limit) of 0.1%
3. Supplementary labeling statement for corrosion to the respiratory tract EUH071
4. SCL for STOT SE3

Environmental

1. M factor of 10 for the acute aquatic toxicity is no longer applicable.
2. General Environmental comments

ECHA's note: The information above was provided in:
Industry comments on the Proposed Harmonized Classification of Glutaraldehyde [Attachment 1]

Dossier Submitter's Response

Thank you for your comments.

Human health

The dossier submitter does not agree with comments given regarding classification for Acute Tox 1; H330, Skin Sens 1A; H317 and assignment of EUH071.

The dossier submitter agrees with the comments regarding SCL for STOT SE 3.

Please, see our response to the comments number 8, 10 and 19.

Environment

The dossier submitter has revised the classification proposal due to new information received during the public consultation period. The dossier submitter proposes the following environmental hazard classification for glutaraldehyde according to the Regulation (EC) No 1272/2008 (CLP):

Aquatic Acute Category 1, **with M-factor of 1**; H400 'Very toxic to aquatic life'

Aquatic Chronic Category 2; H411 ' Toxic to aquatic life with long lasting effects'

Regarding general environmental comments, the CHL Report is a proposal from the dossier submitter and, according to current RAC procedure, cannot be changed at this stage of the process. The concerns mentioned in the comment have been discussed and clarified in the answer for the comment number 26.

RAC's response

RAC agrees with the substitution of the former marine invertebrates test results with the better quality new test results of the same test organism of *Acartia tonsa.* Accordingly, the former marine invertebrates acute toxicity test's result (LC_{50} = 0.07 mg/L), which was the smallest LC_{50}, has been overwritten by the result of the new (GLP) testing with *A. tonsa*: LC_{50} = 3.0 mg/L (nominal). Using the new invertebrates acute toxicity results M factor is M=1, based on the smallest valid acute toxicity result, which is algae ErC_{50} = 0.6 mg/L). It would be of more consequence to use the measured concentration in the report instead of the nominal from the new *A. tonsa* study.
RAC has taken note of the argumentation by the companies regarding the Acute Tox 1. classification. Please see the responses to comment no. 12.

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2013	Germany		MemberState	2

Comment received

The DE CA supports the removal of the asterisk from Acute Tox. 3; H301 and tightening the classification for the inhalation route from Acute Tox. 3; H331 to Acute Tox. 1; H330 using the classification limit for vapour. DE furthermore asupports the additional classification as Aquatic Chronic 2; H411. In addition, DE proposes classification as Category 2 mutagen; H341.

Dossier Submitter's Response

Thank you for comments and support.
Regarding mutagenicity, we have considered classification for mutagenicity and this is also stated in the CLH dossier. However our conclusion is that we propose no classification based on inconclusive data. If in the future the information requirements in the biocide legislation change such that the site of contact genotoxicity should be examined, then data from those studies could clarify this issue.

RAC's response

RAC agrees with classification as Aquatic Chronic 2; H411.
RAC noted the support from Germany MS regarding Acute Tox 1. Please see response to

comment no. 12.

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2013	France		MemberState	3
Comment received				
FR supports the proposed classification for human health and for environment (Aquatic Acute 1 with M-factor=10 and Aquatic Chronic 2).				
Dossier Submitter's Response				
Thank you for your comments and support. The dossier submitter has revised the environmental hazard classification proposal due to new information received during the public consultation period. Please, see our response to the comment number 26.				
RAC's response				
RAC accepts the revised classification of Aquatic Acute 1 with M-factor=1.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	4
Comment received				
The manufacturing business unit "chemical intermediate" of BASF SE for glutaraldehyde wants to give additional comments to the combined comment of BASF SE and Dow submitted by Team being in charge of the bocidal registration. Basically the chemical intermediates division of BASF SE is in line with the biocides registrants (BASF SE + Dow) but sees the need to provide additional information and arguments in this matter. *ECHA's note: The information above was provided in:* *Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]*				
Dossier Submitter's Response				
Thank you for your comments. **Human health** The dossier submitter does not agree with comments given regarding classification for Acute Tox 1; H330 and assignment of EUH071. The dossier submitter agrees with the comments regarding SCL for STOT SE 3. Please, see our response to the comments number 8 and 10. **Environment** The dossier submitter has revised the environmental hazard classification proposal due to new information received during the public consultation period. Please, see our response to the comments number 5 and 26.				
RAC's response				

RAC accepts the revised classification of Aquatic Acute 1 with M-factor=1. Other arguments are discussed in the response to Comment No 26.
Regarding Acute Tox 1, please see response to comment no. 12.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	5

Comment received

1) Proposed classification change Environment:
Directive 67/548/EEC: N; R50: C ≥ 2,5 % ;
CLP Regulation: M-factor M=10 to Aquatic Acute 1 Aquatic Chronic 2
Comment
Algae toxicity would be the preferred reason for new classification. However classification change reflects the data of glutaraldehyde. No further comment

2) Proposed classification change Toxicology:
Directive 67/548/EEC: T+; R26
CLP Regulation: Acute Tox 1; H330, Removal of asterisk (*) from Acute Tox 3: H301
Comment:
Suggestion based on aerosol classification should be:
Directive 67/548/EEC: T; R23
CLP Regulation: Acute Tox 2; H330, removal of asterisk (*) from Acute Tox 3
H301; EUH071 (corrosive to the respiratory tract)

ECHA's note: The information above was provided in:
Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]

Dossier Submitter's Response

Thank you for your comments.

1. Environment

The dossier submitter has revised the environmental hazard classification proposal due to new marine crustacean *Acartia tonsa* study received during the public consultation period. Consequently, the algae *Scenedesmus subspicatus* is the most sensitive species with ErC50 of 0.6 mg/l and M-factor of 1 is applicable (0.1 < LC50 ≤ 1 mg/l), in contrast with the previous proposal (According to the criteria an M-factor of 10 was applicable based on *Acartia tonsa* LC50 of 0.07 mg/L, 0.01 < L(E)C50 ≤ 0.1 mg/l.)
In conclusion, the dossier submitter proposes the following environmental hazard classification for glutaraldehyde according to the Regulation (EC) No 1272/2008 (CLP):

Aquatic Acute Category 1, **with M-factor of 1**; H400 'Very toxic to aquatic life'

Aquatic Chronic Category 2; H411 ' Toxic to aquatic life with long lasting effects'

Please, see also our response to the comment number 26.

2. Human health

The dossier submitter does not agree with comments given regarding classification for Acute Tox 1; H330 and assignment of EUH071.
Please see our response to the comments number 8 and 10.

RAC's response
RAC agrees with the revised environmental classification: Aquatic Acute Category 1, **with M-factor of 1**; H400 'Very toxic to aquatic life' and Aquatic Chronic Category 2; H411 'Toxic to aquatic life with long lasting effects'. Regarding Acute Tox 1, please see response to comment no. 12.

MUTAGENICITY

ECHA note: Two comments were received regarding mutagenicity. No data were presented in the CLH report on mutagenicity and no classification was proposed. The comments and responses to them by the Dossier Submitter and RAC are included below for transparency but mutagenicity will not be addressed in the RAC Opinion.

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2013	Germany		MemberState	6
Comment received				
p. 68: DE proposes classification as Category 2 mutagen; H341 according to Regulation (EC) No 1272/2008. GA is clearly positive in vitro and equivocal in vivo. However, significance of in vivo studies is limited because evaluated tissues might not have been adequate (e.g. Doc IIA, CAR Glutaraldehyde). From the genotoxic potential shown in vitro at least site of contact mutagenicity is to be expected. This is also in accordance with other aldehydes (e.g. formaldehyde). According to Regulation (EC) No 1272/2008 chapter 3.5.2.2, „substances which are positive in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens shall be considered for classification as Category 2 mutagens". According to the Guidance on the application of the CLP criteria" (chapter 3.5.1) 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". Hence, the endpoint of mutagenicity should be addressed in the dossier.				
Dossier Submitter's Response				
Thank you for your comments. Regarding mutagenicity, we have considered classification for mutagenicity and this is also stated in the CLH dossier. However our conclusion is that we propose no classification based on inconclusive data. If in the future the information requirements in the biocide legislation change such that the site of contact genotoxicity should be examined, then data from those studies could clarify this issue.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	7
Comment received				
Finnish position supported by the lead registrant: Non-classification of germ cell mutagenicity The position of Finnish CA that the evidence was not sufficient for classification glutaraldehyde as category 2 germ cell mutagen is supported. As concluded by the Finnish CA the risk to humans was considered sufficiently covered based on the negative results of the carcinogenicity and reproductive toxicity studies. The Finnish CA stated that glutaraldehyde may not have reached the target tissue in the in-vivo mutagenicity studies due to its reactivity. This statement can be used in two directions. If glutaraldehyde				

is supposed not to reach the target tissue in in-vivo mutagenicity studies than it cannot reach gonads to cause germ cell mutagenicity as well (= no classification for germ cell mutagenicity supported regardless the reason behind it).
At the site of contact glutaraldehyde is caustic which means tissue destruction, cell death, respectively. Consequently it is proven that in practice no mutagenic hazard of glutaraldehyde for humans is to be expected.

ECHA's note: The information above was provided in:
Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2013	Germany		MemberState	8

Comment received

DE supports the proposed classification STOT SE 3; H335. But concerning labelling the additional assignment of the EUH071 is in our opinion somewhat inconsistent. Are there any "SCLs" for this assignment to mixtures intended? However, the quantitative derivation of the proposed SCL is not plausible because the irritation threshold of approx. 0.5 ppm glutaraldehyde in air does not necessarily mean that just 0.00005 % in a preparation is the appropriate benchmark for mentioning possible respiratory irritation.

Dossier Submitter's Response

Thank you for your comments. The dossier submitter disagrees with the comments on EUH071 and agrees with the comments on STOT SE 3 and SCL.

STOT SE 3 and SCL
We see the points of the comments on our proposal to set a low SCL for STOT SE 3; H335 for glutaraldehyde.

It is generally considered that sensory irritation near triggering concentrations is a physiological and not toxic response in that no tissue damage or cellular injury is involved. Sensory irritation encompasses a graded series of responses generally categorized as ranging from slight to moderate to severe (Golden 2011). It is known for some aldehydes such as formaldehyde that sensory irritation precedes tissue damage (Golden, 2011). According to Arts et al. (2006), "It is very important to note that recognition or awareness of a compound in itself is not an adverse effect but the degree of sensory irritation to be classified as adverse should be established."

Regarding human data on the perception of respiratory tract irritation, it is known that the odor of an irritant may be a confounding factor (Arts et al. 2006, Golden 2011). According to the CLP criteria on respiratory tract irritation, "ambiguous reports simply of irritation in humans should be excluded since this subjective perception can be confounded by e.g. odor" . However, distinction between olfactory and trigeminal stimulation can be made by using methods excluding subjective irritation symptoms.

In the study on human volunteers using glutaraldehyde it was possible to distinguish the

thresholds for odor perception and sensory irritation (Cain et al. 2007). The sensory irritation threshold of 0.39 - 0.47 ppm match with the result from the Alarie test on mice (RD10 0.4 ppm; Werley et al. 1995). It was not in the scope of those studies to examine the cytotoxicity effect of glutaraldehyde in the respiratory tract.
When does the sensory irritation become an adverse effect (pathological irritation) and a toxicologically relevant endpoint for aldehydes such as glutaraldehyde? It has been reported that glutaraldehyde levels of 0.3-0.5 ppm have caused effects on the nasal mucosa in mice and rats in short term studies (9-12 days; Ballantyne and Jordan, 2001). In an acute inhalation toxicity study at single dose level of 27 ppm GA (0.11 mg/l, exposure time 4 h) there were no mortalities however necropsy findings at day 14 included rhinitis and goblet cell hyperplasia in the nasal cavity (Dow A6.1.3/2). In other acute inhalation studies cytotoxic effects were not reported. Human occupational data on glutaraldehyde-evoked respiratory tract irritation is somewhat ambiguous since only subjective reports of irritation are described and the exact exposure levels are not known. In general, the exposure levels were slightly below or well above 50 ppb. Thus, the human data can only serve as part of weight of evidence.

How to convert ppm in air to concentration limits for mixtures is not clear. There is no guidance available and therefore we cannot provide calculations how to derive SCL. To give some perspective to the respiratory tract irritation classification (R37 and STOT SE 3; H335) and the assigned SCLs, we have compared a few aldehydes (glutaraldehyde, formaldehyde and acetaldehyde) with harmonized classifications. In addition, comparison is made in terms of parameters of sensory irritation and odor thresholds, tissue damage and OELs (table 1). The data behind classification as R37 and setting of SCLs was not available to the DS. The harmonized classification of formaldehyde for corrosion was added in the 22nd ATP of the DSD, and the harmonized classification of acetaldehyde was added in the 12th ATP. Harmonized classification for glutaraldehyde was added in the 29th ATP of DSD.

Table 1. Comparison of selected aldehydes regarding their classification and thresholds relevant for respiratory tract irritation.

Substance	**Classification**	**SCL**	**Odor threshold, ppm**	**Sensory irritation threshold (humans, objective methods), ppm**	**Tissue damage (cytotoxicity, animals), ppm**	**OEL, ppm (based on irritation)**
Glutaraldehyde	Skin Corr. 1B	Skin Corr. 1B: C ≥ 10% STOT SE 3: C ≥ 0.5%	0.0003 [a] 0.04 [b]	0.39-0.47 [a] 0.3 [e]	≥ 0.3-0.5 [e]	0.05 [e, i]
Formaldehyde	Skin Corr. 1B	Skin Corr 1B: C ≥ 25% STOT SE 3: C ≥ 5%	0.05-0.18 [c]	1.7 [c]	≥ 2-3 [c, g]	0.2 [j]
Acetaldehyde	STOT SE 3 [Not classified	No SCL, GCL of 20	0.05 [d]	> 50 [f]	>500 [h]	25-100 [k] 50 [l]

	for skin corrosion]	% applies				

a Cain et al. 2007
b Nayebzadeh 2007
c Arts et al. 2006
d WHO, IPCS
e Ballantyne and Jordan, 2001
f Muttray et al. 2009
g Golden, 2011
h Dorman et al. 2008
i 2012. Substance Overview for Glutaraldehyde. The MAK Collection for Occupational Health and Safety. 1.
j SCOEL of formaldehyde
k Carex Canada. http://www.carexcanada.ca/en/acetaldehyde/#occupational_exposures
l 2013. Acetaldehyde [MAK Value Documentation, 2013b]. The MAK Collection for Occupational Health and Safety. 1–58.

Of the three aldehydes in table 1, glutaraldehyde is the most potent corrosive substance and respiratory tract irritant and acetaldehyde is the weakest with formaldehyde lying somewhere in the middle. This potency order is reflected in the present classification for skin corrosion and in the SCL for respiratory tract irritation.

Taken together, based on the aforementioned reasoning in table 1, we shall withdraw our proposal for the SCL of 0.0005% and propose to retain the existing SCL of 0.5 % for glutaraldehyde.

References:

Arts JHE, de Heer C and Woutersen RA. Local effects in the respiratory tract: relevance of subjectively measured irritation for setting occupational exposure limits. Int. Arch. Occup. Environ. Health. 79: 283 (2009)

Ballantyne B and Jordan SL. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures. J Appl. Toxicol. 21: 131 (2001)

Cain WS, Schmidt R and Jalowayski AA. Odor and chemestesis from exposures to glutarladehyde vapour. Int. Arch. Occup. Environ. Health. 80: 721 (2007)

Dorman DC, Struve MF, Wong BA, Gross EA, Parkinson C, Willson GA, Tan YM, Campbell JL, Teeguarden JG, Clewell HJ 3rd and Andersen ME. Derivation of an inhalation reference concentration based upon olfactory neuronal loss in male rats following subchronic acetaldehyde inhalation. Inhal. Toxicol. 20: 245 (2008)

Golden R. Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazard. Crit. Rev. Toxicol. 41: 672 (2011)

IPCS ENVIRONMENTAL HEALTH CRITERIA 167. ACETALDEHYDE. World Health Organization, Geneva, 1995 http://www.inchem.org/documents/ehc/ehc/ehc167.htm

Muttray A, Gosepath J, Brieger J, Faldum A, Pribisz A, Mayer-Popken O, Jung D, Rossbach B, Mann W and Letzel S. Noacute effects of an exposure to 50 ppm acetaldehyde on the upper airways. Int. Arch. Occup. Environ. Health. 82: 481 (2009)

Nayebzadeh A. The effect of work practices on personal exposure to glutaraldehyde among health care workers. Ind. Health. 45: 289 (2007)

SCOEL/SUM/125 March 2008. Recommendation from scientific committee on occupational exposure limits for formaldehyde.

Werley MS, Burleigh-Flayer HD and Ballantyne B. Respiraory peripheral sensory irritation and hypersensitivity studies with glutaraldehyde vapour. Toxicol. Ind. Health 11: 489 (1995)

2012. Substance Overview for Glutaraldehyde. The MAK Collection for Occupational Health and Safety. 1.

2013. Acetaldehyde [MAK Value Documentation, 2013b]. The MAK Collection for Occupational Health and Safety. 1–58.

EUH071
According to the CLP criteria in Annex I, Note 1 in Table 3.1.3, the supplementary H-statement EUH071 is assigned to substances whose mechanism of acute inhalation toxicity is corrosivity. Therefore the proposal to assign EUH071 to glutaraldehyde is justified. There are other recent cases where a similar solution has been undertaken (eg. acrolein).

RAC's response
RAC agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	9

Comment received

Finnish position supported by the lead registrant: Non-classification as respiratory sensitizer cat 1a)
The Finnish position that the existing data is not supporting to classify glutaraldehyde as a respiratory sensitizer of category 1a is supported. The position that the presented human data on respiratory sensitization might be considered pointing towards a subcategory 1b is supported as well. An atmosphere of 50 ppb glutaraldehyde is non-irritating which was explained in the CLH dossier in detail. Furthermore the CHL dossier gives great support to the conclusion that 50 ppb is a concentration at which respiratory sensitization can be excluded for humans as well.

ECHA's note: The information above was provided in:
Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]

Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Switzerland	Dow Benelux B.V. and BASF SE	Company-Manufacturer	10

Comment received

Acute Tox 1; H330 for inhalation

The applicants agree that the relevant acute inhalation study cited gives an LC50 of 0,35 mg/l in male rats and 0.28 mg/l in female rats (4h exposure). However the report's description 'very fine aerosol > 0.28 µm or as a vapor' was not precise from today's perspective. Thus as stated, a physicochemical study was conducted representing the conditions of the animal test and indicating that the vapor phase accounted for 65 to 68% of glutaraldehyde. However one key sentence of the respective report is missing in the dossier:

"*Thus one can assume that liquid aerosols were also present in the animal studies cited. Protectol GA 50 (50 % aqueous glutaraldehyde) has a saturated vapor concentration (SVC) around 0.35 mg/L air. It is noteworthy that water also contributes to the vapor concentrations measured, thus the amount of glutaraldehyde in the vapor will be lower." Due to the significant fraction of liquid aerosol at LC50 concentration, the test substance should be classified as aerosol based on the data of this technical trial.*"

This is clearly supported by the inhalation risk test being a part of the BPD dossier (A6.1.3_03) following OECD 403 TG from May 1981 and using also 50% aqueous glutaraldehyde solutions as test compound. Note that higher concentrations than this are not achievable as glutaraldehyde polymerizes and is unstable. This test examined the mortality and clinical symptoms of rats exposed to a saturated vapour atmosphere at 20°C for 1, 3 or 7 hours followed by a 14 day observation period. There was no mortality when 12 rats were exposed for 1 hour and one out of 12 rats died after exposure for 3 hours (8% mortality). After 7 hours of exposure all 6 rats used for this experimental part died. Thus it can be reasonably assumed that mortality in the range of the LC50 is predominantly caused by aerosol and not by vapour. Thus the classification limits of an aerosol should apply. This would result in acute Tox 2 H330 for inhalation.

ECHA's note: The information above was provided in:
Industry comments on the Proposed Harmonized Classification of Glutaraldehyde [Attachment 1]

Dossier Submitter's Response

Thank you for your comments. The dossier submitter does not agree with comments given regarding classification for Acute Tox 1 and thus retains the previous opinion on Acute Inhalation Toxicity category, i.e. Acute Tox 1.

I. FI as the RMS under the BPD received a simulation study (also referred to as a physicochemical study in comment 10, as the study of Wittmer (BASF 2012) in comment 11 and as Project No.: 12I0674/05I015 in comment 12). Data in the document suggests that both vapor and liquid aerosol exist in significant proportions in conditions relevant to earlier animal testing, especially the study A6.1.3.1. However, the reliability of this simulation

study could not be assessed as only a summary report was submitted. Other weaknesses observed include 1) uncertainty on which concentrations were derived by calculation, 2) a qualitative claim only on contribution of water in vapour concentrations, even if a reasonable one, and 3) a significant, about 30 years, distance to the experimental part of most related animal study (A6.1.3.1.).

Even if both vapor and liquid aerosol existed in significant proportions according to this trial (ca two thirds as vapour form and one third as liquid aerosol at the total concentrations around the LC50; e.g. the tabled values of ca 0.2 mg/L as vapor and 0.1 mg/L as liquid aerosol, at the total concentration of ca. 0.3mg/L), and even if we see the both physical forms possible, we cannot agree with the argumentation on using criteria of mists for classification. This is discussed in more detail as follows:

In comment 10, and in related comments on the biocide assessment, it is proposed by companies that criteria for mists should be applied due to a significant fraction of liquid aerosol at LC50 concentration. In the comment they refer to ECHA guidance (Guidance on the application of CLP criteria) and argue that based on the Guidance an LC50 close or above the Saturated Vapour Concentration (SVC) will be considered for classification in the criteria for mists. It was stated in the comment 10 that the SVC for 50 % glutaraldehyde in water, 0.35 mg/L, should be used as the value in comparison with the LC50. (*Our minor technical comment on the value of 0.35 mg/L is that it would be rather the value of 0.53 mg/L that is the mathematically correct value within reasoning of the commenting company, based on vapour pressure of 0.13 hPa, found also in comment 12*).

We cannot agree with the position in comment 10, because the concentration of vapour at concentrations relevant to LC50 is significant (possibly even two thirds of total, see above) and it is also well within the Cat 1 relevant range for vapours, and it is also clearly below the extrapolated SVC of pure glutaraldehyde (1.8 mg/L). The most critical LC50 is 0.28 mg/L (A6.1.3.1).

Here we would also like to express the following:
- In page 264 of the Guidance on the Application of the CLP Criteria Version 4.0 – November 2013, it is stated that **'An LC50 well below the SVC will be considered for classification according to the criteria for vapours; whereas an LC50 close to or above the SVC will be considered for classification according to the criteria for mists** (see also OECD GD 39).'
-The lines from Guidance, above, can also be given a minor comment, even if it is not decisive here, that is our understanding that SVC and its relationship to physical forms vapour and mist (aerosol) in this context are meaningful for a single substance for whether it has reached vapour saturation concentration. In the case of glutaraldehyde, the case is more complex and partially characterized, the aerosol fraction possibly resulting more from the way the test atmosphere is created and not resulting from approaching saturation of vapour. It remains somewhat uncertain whether the SVC concept can be fully applied here. If it is applied, we think it is more relevant to in assessing the (sub)saturation of vapor, and of a single component.

II: The A6.1.3_03 study, referred to in comment 10 and in comment 11 (as study report 80/265), cannot be considered reliable due to several major deficiencies. Also we think that consideration should be given to the high number of mortalities (100 %) after exposure of 7 hours.

III. Conclusions: Due to lack of high quality data and due to complexities in physical forms in test atmosphere, uncertainties remain.

Based on our earlier opinion and the observations above we are of the opinion that our proposal for Acute Tox 1 is on a more solid basis than the one in comment 10 and in related comments.
Several lines of argumentation and information may give a fuzzy picture, but **we emphasize that criteria for classification should be based on concentration of vapour form of glutaraldehyde as the vapour form likely exists at a significant, possibly even dominant, proportion at concentrations of LC50. The fact that this glutaraldehyde vapour in test atmosphere is well below vapour saturation of glutaraldehyde further supports criteria for vapour**.

RAC's response
Please see the response to comment no. 12.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	11
Comment received				

Classification for Inhalation toxicity
The chemical intermediates division of BASFSE **strongly disagrees** with the proposal to classify glutaraldehyde as **acute tox. inhal. Cat.1 classification is not in line with the classification criteria** given in the CLP regulation (1272/2008/EC). Aerosol criteria have to be applied for Glutaraldehyde.
The study of Wittmer (2012, BASF) is one of the key studies for correct classification of glutaraldehyde:
1) Consequently, a robust study summary should be included in the CLH dossier.

2) Furthermore the result of this study should be cited completely:

"*Thus one can assume that liquid aerosols were also present in the animal studies cited. Protectol GA 50 (50 % aqueous glutaraldehyde) has a saturated vapor concentration (SVC) around 0.35 mg/L air. It is noteworthy that water also contributes to the vapor concentrations measured, thus the amount of glutaraldehyde in the vapor will be lower. Due to the significant fraction of liquid aerosol at LC50 concentration, the test substance should be classified as aerosol based on the data of this technical trial." (citation of the study report Wittmer; 2012)*
The result was already explained in detail (see comment of 21.06.2012 to the dossier submitter attached in the annex of this comment)
As explained there a water contamination always contributes to the measured vapor concentration but not to the measured aerosol concentration. Consequently, glutaraldehyde vapour in any atmosphere from 50% glutaraldehyde is an overestimation, which is not negligible but hard to prove. One can imagine overestimation by comparison of the vapour
pressure of water (23.94 hPa @ 20°C), 50% aqueous glutaraldehyde solution (21.9 hPa @ 20°C BASF; 1983) and partial vapour pressure of 50% glutaraldehyde in water (0.13 hPa @ 20°C; Olsen 1995).
Consequently, it should be added on page 15 & 31 that the conclusion: "At measured concentrations of 0.224 and 0.34 mg/L, the vapour phase accounted for 65 and 68 % of the glutaraldehyde, respectively" is still an overestimation of the glutaraldehyde vapour as water is still contributing to the vapor concentration. Therefore it is the conclusion that glutaraldehyde should be treated as vapor in the classification procedure consequently is incorrect, as glutaraldehyde vapour concentration can be expected to be lower than 50 %. Especially, in the light of the main conclusion of the study report that technical achievable saturated vapour concentration of glutaraldehyde is around 0.34 mg/L. That is the reason why the report concluded: "… *the test substance should be classified as aerosol based on the data of this technical trial."*
3) Furthermore, there is clear scientific weight of evidence that it is the aerosol causing mortality and consequently aerosol criteria should apply for classification of inhalative toxicity. a. Taking a broader look

at the 2 key studies: Both studies have been conducted in the early 1980's (probably 1980, 1983) in the same laboratory. Mortality rates at a given concentration are comparable and giving a clear cut at the technically achievable vapour saturation concentration, which is logical. Local exposure of the lung tissue changes dramatically at vapor saturation concentration from diffuse low exposure of a vapor to a spotted concentrated exposure of caustic glutaraldehyd droplets on the lung tissue:

Study 83/59	Study 80/265
0.22 mg/L ➔ 0/20 animals	0.18 mg/L ➔ 4/20 animals
0.31 mg/L ➔ 3/20 animals	0.31 mg/L ➔ 4/20 animals
Technical achievable vapor saturation 0.35 mg/L	
	0.39 mg/L ➔ 14/20
0.63 mg/L ➔ 15/20	0.44 mg/L ➔ 19/20

b. As already stated in earlier comment the existing Inhalation hazard test provides clear scientific evidence that glutaraldehyde vapor is not the relevant toxic component in an glutaraldehyde atmosphere (see Inhalation hazard test part in study report 80/265). This test is described in the Annex of OECD 403 Method for demonstration of the toxicity of an atmosphere saturated with vapours of the volatile components of a test substance at a temperature chosen for vapour generation, usually 20°C. This test describes the risk of mortality to the practically achievable saturated vapour atmosphere. In principle, groups of rats of both sexes are sequentially exposed to the vapours, generated by bubbling 200 l/h air through a substance column of about 5 cm above a fritted disc in a glass cylinder for different time periods. The exposure time not causing lethality was usually tested twice. In this test system the aerosol does not reach the inhalation chamber. The theoretical nominal test concentration calculated from substance loss was reported as 15 mg/L. Substance loss is however summing up vapour plus aerosol. Never the less animals can be expected to have been exposed to a vapor close to the saturated vapor concentration of 0.35 mg/L. One of the 6 male and 6 females rats exposed for 3 hours to this atmosphere saturated with 50% glutaraldehyde vapour at 20 °C died. This study demonstrates that there is no risk of mortality from vapour arising from a 50% glutaraldehyde solution is low compared to the risk arising from glutaraldehyde aerosol. From a weight of evidence perspective this study gives as well relevant key information for finding the correct classification of glutaraldehyde and consequently should be described in the CHL dossier. Furthermore this study is as well a part o the study report 80/265 and should be as well mention for formal reasons (completeness).
(Remark: unfortunately in the comment of 21.06.2012 a study with 25% glutaraldehyde was described).

ECHA's note: The information above was provided in:
Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]

Dossier Submitter's Response

Thank you for your comments. The dossier submitter does not agree with comments given. Please see our response to the comment number 10.

RAC's response

Please see the response to comment no. 12

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	12

Comment received

Rational
a) Aerosol

Considering 50% glutaraldehyde as vapour in the inhalative toxicity studies and classifying as acute tox 1; H330 is not warranted as glutaraldehyde in the inhalation studies is almost completely an aerosol. This evaluation requires careful analyses as follows: This is not seen very easily and there have been incorrect assumptions and statements in the on-going discussion.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLUTARAL; GLUTARALDEHYDE; 1,5-PENTANEDIAL

1) Calculation of the vapour saturation of the RMS is based on wrong assumptions.

SVC [mg/l] = 0.0412 x MW x vapour pressure in hPa at 20°C
SVC = 0.0412 x 100.11 x 0.44 hPa = 1.81 mg/L
The RMS calculation used the vapour pressure of 100 % glutaraldehyde. However glutaraldehyde interacts with water. This has an influence on the vapour saturation concentration (SVC) as water-glutaraldehyde action lowers partial vapour pressure. Partial vapour pressure of glutaraldehyde in a 50% aqueous solution is 0.13 hPa (see Olson 1998).
Consequently theoretical SVC is: SVC_{th} = 0,0412 x 100,11 x 0.13 hPa = 0.53 mg/L

2) New BASF Study Project No.: 12I0674/05I015
In this study a "practical achievable saturated vapour concentration" of a 50% glutaraldehyde solution for inhalation studies was determined.
A test atmosphere in an inhalation study is generated by a two-component atomizer by means of a metering pump. This means a continuous flow of liquid is sprayed into a continuous flow of air. This generates an aerosol. However, due the large surface of the micronized respirable aerosol some liquid may evaporate and instead of a pure aerosol an aerosol/vapour mixture is led into the exposure chamber. However, as time for evaporation is limited theoretical saturated vapour concentration is practically never reached for substances with a low vapour pressure.
The practical achievable saturated vapour concentration of a 50 % glutaraldehyde solution was determined in Project No.: 12I0674/05I015 to be in the range of 0.35 mg/L if one generates a 0.9 mg/L atmosphere. This was the nominal concentration in the BASF inhalation studies.
However, besides the analytical data the following aspects are important for a valid evaluation and conclusion.

3) Experimentally it was determined that a test atmosphere of 0.9 mg/L glutaraldehyde solution contains 0.35 mg/L vapour. The most important sentences in the conclusion of the project report however is:
"It is noteworthy that water also contributes to the vapour concentrations measured, thus the amount of glutaraldehyde in the vapour will be lower."
Consequently 0.35 mg/L glutaraldehyde vapour in an atmosphere of 0.9 mg/L 50% glutaraldehyde is still an overestimation which is not negligible but hard to prove. But one can imagine overestimation by comparison of the vapour pressure of water (23.94 hPa @ 20°C), 50% aqueous glutaraldehyde solution (21.9 hPa @ 20°C BASF; 1983) and partial vapour pressure of 50% glutaraldehyde in water (0.13 hPa @ 20°C; Olsen 1995).

B) Risk of mortality
Another strong argument that aerosol is to be considered for estimation of inhalative toxicity of 50% glutaraldehyde is the inhalation hazard test. This test is described in the Annex of OECD 403 Method for demonstration of the toxicity of an atmosphere saturated with vapours of the volatile components of a test substance at a temperature chosen for vapour generation, usually 20°C. This test describes the risk of mortality to the practically achievable saturated vapour atmosphere.
In principle, groups of rats of both sexes are sequentially exposed to the vapours, generated by bubbling 200 l/h air through a substance column of about 5 cm above a fritted disc in a glass cylinder for different time periods. The exposure time not causing lethality was usually tested twice. In this test system the aerosol does not reach the inhalation chamber. None of the male and females rats exposed for 8 hours to this atmosphere saturated with 50% glutaraldehyde vapour at 20 °C died. The theoretical nominal test concentration calculated from substance loss was reported as 40 mg/L. Substance loss is however summing up vapour plus aerosol.
This study demonstrates that there is no risk of mortality from vapour arising from a 50% glutaraldehyde solution. Substance loss shows that practically only aerosol was generated under test conditions, and that the amounts of vapour that may have been generated are acutely non-lethal.
Summary
It has been demonstrated that the 50 % glutaraldehyde tested has to be regarded as aerosol in its inhalative toxicity studies.
Beyond this, it has been demonstrated that there is no risk of mortality from vapours arising from a 50% glutaraldehyde solution which is the highest technical achievable concentration.
Consequently correct classification of inhalative toxicity is Acute Tox 2; H330 (CLP regulation 1272/2008) and T; R23 (Directive 67/548/EEC).

ECHA's note: The information above was provided in:
Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]

Dossier Submitter's Response

Thank you for your comments. The dossier submitter does not agree with comments given. Please see our response to the comment number 10.

RAC's response

In a 50 % aqueous solution of glutaraldehyde, the Saturated Vapour Concentration (SVC) cannot be calculated using the vapour pressure of 100% glutaraldehyde. The partial vapour pressure in a 50% solution is given to be 0.13 hPa for glutaraldehyde (Olsen, 1995) instead of the standard 0.44 hPa.

A theoretical SVC for glutaraldehyde in a 50% aqueous solution can then be calculated as 0.0412 x 100.11 (g/mol) x 0.13 hPa. This results in 0.53 mg/L. But in practice this will only occur in an environment completely saturated with glutaraldehyde.

In order to clarify whether the test substance should be considered as an aerosol or vapour, the applicant under the biocidal active substance process performed a physical/chemical study mimicking the system used in the inhalation study. At measured concentrations of 0.224 and 0.349 mg glutaraldehyde/L the vapour phase accounted for around 66%. That means that two-thirds of the glutaraldehyde is presented as vapour. To take this assumption further, the saturated partial glutaraldehyde vapour phase will then be around two-thirds of 0.53 mg/L = 0.35 mg/L as determined in the physical/chemical study.

The LC50 values obtained from the inhalation studies are within the range 0.28 mg/L to 0.52 mg/L. In the guidance it is stated that *"A LC50 well below the SVC will be considered for classification according to the criteria for vapours; whereas an LC50 close to or above the SVC will be considered for classification according to the criteria for mists".*

RAC concludes that the SVC is close to the LC50 values, and therefore classification for glutaraldehyde should be according to the aerosol criteria and not the criteria for vapour.

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	France		MemberState	13

Comment received

In addition to our support for the general proposal, FR has the opinion that specific concentration limit for acute inhalation toxicity could be suggested. Indeed, we agree that the calculated value (4 %) is close to the general concentration limit of 7% for R26; nevertheless, this threshold could impact the risk management for the product. Classification T+; R26 induces wearing of PPE whereas for T; R23 or Xn; R20 no PPE is required.

Dossier Submitter's Response

Thank you for your comments. We think that the calculated value of 4% is so close to the general concentration limit of 7% that no SCL is needed. In addition, by the time the updated entry for glutaraldehyde is included in the Annex VI of the CLP Regulation, the DSD and DPD are repealed and there is no need to harmonize the entries according to them.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Belgium		MemberState	14
Comment received				
We would you like to thanks Finnish Competent Authority for the CLH report on glutaraldehyde. We support the proposal to reclassify glutaraldehyde based on the results of the inhalation acute toxicity studies. The two key studies, according to OECD guideline 403, show a LC50 between 0.28 and 0.52 mg/l, which fulfills the criteria for category 1 (LC50≤0.5mg/l). We support the removal of asterisk from Acute Toxicity category 3 via the oral route due to the results of the 2 key studies showing a LD50 between 50 and 300 mg/kg bw/d : ☐ In the Dow study , with the test substance of 50% glutaraldehyde, mortalities are observed and indicate a LD50 of 246 mg/kg bw for male and 154 mg/kg bw for female. ☐ In the BASF's study, the results show, also for 50% glutaraldehyde, a LD50 of 316 mg/kg bw for male and 285 mg/kg bw for female. For the acute dermal toxicity, we question the rational of the DS to reject the Dow study which is reported as a key study in the dossier. The results show a LD50 of 1750 mg/kg with a test substance of 50%. Besides, the effects observed are quite severe : red lungs, dark spleens, intestine opaque, mottled, red and light red or tan liver and kidneys.				
Dossier Submitter's Response				
Thank you for your comments and support. Regarding acute dermal toxicity the LD_{50} value derived from the study in question (Dow A6.1.2) was not considered reliable since the animals (rabbits) were immobilized for 24 h during treatment with a corrosive substance and thus higher mortality could be due to the poor treatment. We gave more weight to the other two dermal toxicity studies where lower or no mortality was observed.				
RAC's response				
Noted. RAC agrees with the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2013	Germany		MemberState	15
Comment received				
DE supports the removal of the asterisk from Acute Tox. 3; H301 and tightening the classification for the inhalation route from Acute Tox. 3; H331 to Acute Tox. 1; H330 using the classification limit for vapour.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. Regarding acute inhalation toxicity, please see our response to comment no. 12.				

OTHER HAZARDS AND ENDPOINTS – Irritation/Corrosion

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Switzerland	Dow Benelux B.V. and BASF SE	Company-Manufacturer	16
Comment received				
Supplementary labelling statement for corrosion to the respiratory tract EUH071				

Other substances classified as STOT SE3 and considered corrosive to the skin/eye do not carry such an EU phrase. The classification of Toxic by Inhalation H330 based on local, upper respiratory tract effects in addition to STOT SE3 sufficiently notifies users of the respiratory hazards associated with glutaraldehyde and therefore a EUH071 labelling statement is not necessary. *ECHA's note: The information above was provided in:* *Industry comments on the Proposed Harmonized Classification of Glutaraldehyde [Attachment 1]*
Dossier Submitter's Response
Thank you for your comments. The dossier submitter disagrees with the comment on EUH071. Please see our response in comment number 8.
RAC's response
RAC agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	17
Comment received				
Supplementary labelling statement for corrosion to the respiratory tract EUH071 As respiratory tract irritation is already included in the current labelling it is superfluous to add EU071 hazard statement. Corrosion and irritation represent the same mode of toxic action. Irritation is a kind of slight corrosion not leading to the destruction of the tissue. Consequently, at low concentrations respiratory irritation is the symptom of substances causing corrosion of the respiratory tract. At high concentrations the corrosion of the respiratory tract leads to death by tissue destruction. Mortality is covered by the acute inhalative toxicity classification. *ECHA's note: The information above was provided in:* *Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]*				
Dossier Submitter's Response				
Thank you for your comments. The dossier submitter disagrees with the comment on EUH071. Please see our response in comment number 8.				
RAC's response				
RAC agrees with the DS.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2013	Germany		MemberState	18
Comment received				
p. 10, table 3: Proposed classification according to the CLP Regulation, 3.2. Skin corrosion / irritation: the proposed classification "Skin Corr. 1B, H314" is missing.				
Dossier Submitter's Response				
Thank you for your comment. The Skin Corr. 1B; H314 is the current classification, therefore it does not appear in the column for "proposed classification".				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Switzerland	Dow Benelux B.V. and BASF SE	Company-Manufacturer	19

Comment received

Skin Sens 1A H317 with a proposed SCL (specific concentration limit) of 0.1%

For the application of subcategory 1A EC regulation 1272/2008 states the application is appropriate for:

„Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests (1). Severity of reaction may also be considered"

There are no reported indications that glutaraldehyde is of significant concern when reviewing sensitization prevalence data that has been published by European dermatology clinics and furthermore no concern has been raised by the dermatological community as to the prevalence of dermatitis associated with handling glutaraldehyde (Aberer et al 2003, Landeck et al 2011). It is also noteworthy that the patch test concentration has been reduced to 0.3% for clinical diagnosis of allergy in order to avoid false positive (non-specific or irritant) reactions observed in the past.

The supporting animal data presented, including that provided by the applicant, indicate that glutaraldehyde is not a potent sensitizer. In an open epicutaneous test, a concentration of 25% was sensitizing to guinea pig skin whereas in several local lymph node assays, the EC3 value reported varies considerably, most likely due to the differing formulations being employed. Further, it is well known that the LLNA assay overestimates sensitization potential for strong irritants such as glutaraldehyde (Ball et al. 2011).

As a result of the above considerations, the presented data is not adequate for subcategorization and the current classification of Skin Sensitizer Category 1 should remain. The wealth of human data obtained using scientific methodology do not support category 1A.

Concerning the concentration limit of 0.1% proposed, the animal data provided does not indicate that glutaraldehyde is a potent sensitizer (as such a reduction in SCL would imply). The current animal and human data support maintenance of the current 0.5% limit.

ECHA's note: The information above was provided in:
Industry comments on the Proposed Harmonized Classification of Glutaraldehyde [Attachment 1]

Dossier Submitter's Response

Thank you for your comment.

We disagree with the comments on Skin Sens. 1A being an inappropriate classification.

The prevalence of contact dermatitis may depend on the useage and exposure patterns of the allergen of concern. Sensitation to glutaraldehyde continues to be relevant in certain occupational areas (e.g. health care personnel, various industries) (Aberer et al. 2003).

In the CLH dossier two different animal studies (GPMT, LLNA) on skin sensitation were described and both of them gave results which justify classification of glutaraldehyde as Skin Sens. 1A according to the CLP criteria (2nd ATP).

Regarding comments on strong irritants giving false positives in the LLNA assay, we can only argue that at least in the GPMT study on glutaraldehyde there were irritation controls which gave negative results. As also shown by Ball et al. (2011) the GPMT assay did not give false positives to the surfactants tested. Glutaraldehyde was not studied in this particular article. We therefore conclude that at least for glutaraldehyde the LLNA test gave a result which is comparable to the GPMT result.

It is true that different formulations gave different EC3 values in the LLNA assay (0.07% and 0.2 % in acetone: olive oil vehicle; 1,5% in PEG) however all of the values are under the limit of the classification criteria for Skin Sens. 1A (for LLNA EC3 ≤ 2 %).

Taken together, we are of the opinion that the results obtained from the GPMT and LLNA assays are true positives and the data justify classification of glutaraldehyde as Skin Sens. 1A.

References:
Aberer W, Komericki P, Uter W, Hausen BM, Lessmann H, Kränke B, Geier J and Schnuch S. Epidemiologische überwachung von kontaktallergenen. Hautarzt 54: 741 (2003)

Ball N. Cagen S, Carrillo JC, Certa H, Eigler D, Emter R, Faulhammer F, Garcia C, Graham C, Haux C, Kolle SN, Kreiling R, Natsch A and Mehling A. Evaluating the sensitization potential of surfactants: integrating data from the local lymph node assay, guinea pig maximization test and in vitro methods in a weight -of -evidence approach. Regul. Toxicol. Pharmacol. 60: 389 (2011)

RAC's response
Noted. RAC agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Belgium		MemberState	20

Comment received
We agree with the proposal to subcategorize the skin sensitization endpoint in 1A based on the followed results : The guinea pig maximization test show a response of 68% at challenge and 32% at re-challenge with an intradermal induction dose of 0.1% of aqueous glutaraldehyde. These results are consistent with the norms of the CLP regulation : skin sensitizer potency strong when concentration for ID induction ≤0.1% and incidence sensitized between 30 and 60%. Besides, the local lymph node assay induce EC3 of 0.07% when glutaraldehyde in acetone:olive oil and 1.5% when glutaraldehyde in propylene glycol and the CLP guidance indicate that a substance is considered as a sensitizer with extreme potency when EC3≤2.
Dossier Submitter's Response
Thank you for the support.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number

05.11.2013	Germany		MemberState	21
Comment received				
Based on the presented data, DE supports the proposal for classification of glutaraldehyde into sub-category 1A for skin sensitisation and removal of the existing SCL.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Switzerland	Dow Benelux B.V. and BASF SE	Company-Manufacturer	22
Comment received				

SCL for STOT SE3

We agree with the assignment of the STOT SE3 classification for glutaraldehyde, however we also note that according to the Guidance on the application of the CLP criteria (ECHA 2012) that for STOT SE cat. 3 no SCL's are foreseen for substances causing respiratory tract irritation as;

"*Classification in STOT-SE Category 3 for RTI and narcotic effects does not take potency into account and consequently does not have any guidance values. A pragmatic default GCL of 20% is suggested.....*".

For example aqueous hydrochloric acid has an assigned SCL of >10% whereas sodium hydroxide has no assigned SCL. We therefore believe the proposed SCL is overly stringent, not in line with EC 1272/2008 version 3.0, (2012) and the data on which it is based does not represent an adverse effect.

According to article 10 EC regulation 1272/2008:

„*Specific concentration limits and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance in another substance or in a mixture as an identified impurity, additive or individual constituent leads to the classification of the substance or mixture as hazardous*".

The proposed SCL relates primarily to the results of the **Cain et al (2007)** study which investigated odour and chemisthesis following glutaraldehyde exposure in human volunteers. This study was designed primarily to look at chemesthetic responses in human volunteers. Chemesthesis is a natural response elicited when certain chemical substances stimulate the trigeminal nerve, it is a normal reflex action, involves no underlying biological/physiological changes and as such cannot be considered adverse.

Further supportive evidence for a reduction in SCL is given by the RMS citing articles describing adverse effects expressed during occupational exposures. Given the limitations of these studies, i.e. lack of relevant exposure measurements during onset of symptoms in the populations studied, we would question the suitability and relevance of such data for deriving a SCL for glutaraldehyde. Furthermore, other regulatory agencies/scientific organisations such as the German MAK/ US ACGIH have reviewed these data in the past and ruled that based on the Cain study a protective value can be set, overruling the inconsistent data reported in the literature.

ECHA's note: The information above was provided in:
Industry comments on the Proposed Harmonized Classification of Glutaraldehyde

[Attachment 1]
Dossier Submitter's Response
Thank you for your comment. The dossier submitter agrees with the comments on STOT SE 3 and SCL. Please see our response to the comment number 8.
RAC's response
Noted. RAC agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Germany		Company-Manufacturer	23
Comment received				
SCL for STOT SE 3 A proposed SCL of 0.00005 % (= 50 ppb) for the classification of mixtures is scientifically not justified. A very detailed description regarding respiratory tract irritation is presented in the CLH dossier. From animal and human data it is concluded that an atmosphere of 13 ppm is clearly causing respiratory tract irritation (RD50). A RD10 of 400 ppb was calculated from this study. This RD 10 fit pretty well with the human study data suggesting some slight irritation 390 -470 ppb. An **atmosphere** of 50 ppb glutaraldehyde is non-irritating which is also underlined by human studies presented in the CLH dossier. However, a **SCL is for the classification of mixtures (liquid in this case)**. Deriving a specific concentration for a breathable atmosphere is the wrong method. It is questionable whether even a 1% glutaraldehyde mixture is able to produce a 50 ppb glutaraldehyde atmosphere. The given description for a NOEC for glutaraldehyde in the air does not provide any scientific evidence to support a lowering of the SCL in mixures (liquids in this case). The existing concentration limit of 0.5% should be maintained therefore. *ECHA's note: The information above was provided in:* *Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde [Attachment 2]*				
Dossier Submitter's Response				
Thank you for your comment. Thank you for your comment. The dossier submitter agrees with the comments on STOT SE 3 and SCL. Please see our response to the comment number 8.				
RAC's response				
Noted. RAC agrees with the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Belgium		MemberState	24
Comment received				
We have some doubts on the classification as STOT SE category 3 H335(may cause respiratory irritation). Indeed, the criteria of the CLP guidance for classifying substances as category for respiratory tract irritation are : respiratory irritant effects (characterized by localized redness, oedema, pruritis and/or pain) that impair function with symptoms as cough, pain, chocking and breathing difficulties. Subjective human observations could be supported by objective measurements of clear respiratory tract irritation. In this case, the study in mouse show a decrease in the respiratory rate but no other effects are observed.				

For the human information, there are variation in the observed effects and the relationship between exposure concentrations/times and effects could not be established with certainty.
Dossier Submitter's Response
Thank you for your comment. The dossier submitter agrees with the comments on STOT SE 3 and SCL. Please see our response to the comment number 8.
RAC's response
Noted. RAC agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
28.10.2013	Germany		Company-Downstream user	25
Comment received				
In the CLH report for glutaraldehyde, page 44 - 4.4.3.5 the SCL of 0,00005% is explained. A concentration of 0.39 - 0.47 ppm for human volunteers of glutaraldehyde in the air! result in a SCL of 0.00005% (concentration in a liquid). And no further explanation?				
Dossier Submitter's Response				
Thank you for your comment. The dossier submitter agrees with the comments on STOT SE 3 and SCL. Please see our response to the comment number 8.				
RAC's response				
Noted. RAC agrees with the DS.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Switzerland	Dow Benelux B.V. and BASF SE	Company-Manufacturer	26
Comment received				

1) Proposed acute environmental classification and M factor

A new acute study on Acartia tonsa was conducted resulting in a LC50 of 3.0 mg/L and was submitted by BASF SE. The full reference is cited and the BPD RSS is attached. This study shows that the toxicity of Acartia tonsa is less sensitive than previously indicated by the old study and the toxicity of glutaraldehyde should now be considered in the same range compared to Daphnia magna. Consequently, Algae is the most sensitive species with an ErC50 of 0.6 mg/L. Therefore, no M-factor has to be applied for acute toxicity of glutaraldehyde.

ECHA's note: Please see Section A7.4.1.2_06 Acute toxicity to invertebrates (non-confidential version) [Attachment 3]

2) General Environmental comments

The applicants disagree with the interpretation of the reporting of the findings on anaerobic degradation and the

aquatic toxicity.

On page 82, the findings on anaerobic degradation are reported as follows:

- "In conclusion, glutaraldehyde is transformed to two persistent metabolites (Compound A and 1, 5-pentanediol) and one intermediate metabolite (5-hydroxy-pentanal) under anaerobic conditions.
- Although persistent metabolites were detected in the anaerobic water/sediment tests, these are not considered relevant for classification purposes."

We do not agree with the current wording and suggest replacing it by:

- Although the metabolites showed indications of persistence under anaerobic conditions, they would be rapidly biodegraded under aerobic conditions. These products would be water soluble with low Kow values, thus partitioning into anaerobic sediments would be limited. Under environmentally realistic conditions, formation of the dimer (Compound A) would be limited since glutaraldehyde would be rapidly diluted, thereby minimizing dimer formation due to unfavourable kinetics. Ultimate biodegradation of glutaraldehyde and its degradation products is expected.

A C & L assessment based on QSAR calculation using EPIWIN only is not recommended, we therefore suggest:

- On pages 82 and 83 to leave the assessment of the anaerobic biodegradation study but to remove the prediction of toxicity and suggestion for classification based on the lack of data.
- On pages 87-88 to remove Table 33 and all corresponding foot notes.

On page 90, we suggest to amend the conclusion as follows:

"Based on partitioning properties, glutaraldehyde is mobile in sandy sediment and moderately mobile in the four studied soils. However, glutaraldehyde will react with available organic matter in soil, therefore glutaraldehyde will be removed in the environment."

The environmental section does not reflect the overall assessment of the hazard studies and key studies provided in the BPD review are not cited in the CLH report:

- Page 94, presents one acute fish study whereas four acute fish studies are available.
- On page 96 and page 99, only data on marine species are presented, but the acute toxicity to *Daphnia* is not reported.
- On page 100, the study on *Ceriodaphnia dubia* is omitted.
- On page 102, two studies with *Scenedesmus subspicatus* are available.

While these studies do not drive the classification, we believe all key studies should be included as a comprehensive summary of aquatic testing in the CLH document.

ECHA's note: The information above was provided in:
Industry comments on the Proposed Harmonized Classification of Glutaraldehyde [Attachment 1]

Dossier Submitter's Response

Thank you for your comments.

1. Proposed acute environmental classification and M factor [see Attachment 1 and 3]
The environmental classification proposal for acute aquatic toxicity was based on a study with marine crustacean *Acartia tonsa* resulting to an LC50 of 0.07 mg/L. According to the criteria an M-factor of 10 is applicable based on 0.01 < L(E)C50 ≤ 0.1 mg/l. However, a new study on marine crustacean *Acartia tonsa* submitted by BASF SE reported an LC50 of 3.0 mg/L. The outcome of the evaluation (based on the data available on BPD robust study summary) by the dossier submitter is that the new study is considered more reliable than the previous study. The old study was conducted under static conditions and measured concentrations declined significantly within 48 hours; values were ranging from 8-33 % of the nominal and the results were based on geometric mean of the measured concentrations, whereas the new study is conducted under semi-static conditions and the concentrations were more stable; measured concentrations were maintained within 80-120 % of nominal concentrations in the concentration range of 0.7-8.1 mg a.s./l.

Consequently, the algae *Scenedesmus subspicatus* is the most sensitive species with ErC50 of 0.6 mg/l and M-factor of 1 is applicable (0.1 < LC50 ≤ 1 mg/l), in contrast with the previous proposal.

In conclusion, the dossier submitter proposes the following environmental hazard classification for glutaraldehyde according to the Regulation (EC) No 1272/2008 (CLP):

Aquatic Acute Category 1, **with M-factor of 1**; H400 'Very toxic to aquatic life'

Aquatic Chronic Category 2; H411 ' Toxic to aquatic life with long lasting effects'

2. General Environmental comments [see Attachment 1]
The CHL Report is a proposal from the Dossier Submitter and, according to current RAC procedure, cannot be changed at this stage of the process. We apologise for the misunderstanding and try to explain the terms used here.

The detailed description of the metabolites occurring in the anaerobic study was added to the CLH report as a response to comments included in RAC Rapporteurs' observation report in Annex III of the Accordance check. In the RAC Rapporteurs' observation report, further information from the point of view of persistency, bioaccumulation and aquatic toxicity was requested for the three degradation products in the anaerobic test (it was noted that all three metabolites exceeded 10% of applied radioactivity). Information on the metabolites occurring in the anaerobic study was thus added to address the comments received, even though it is understood that this information has no effect on the classification of glutaraldehyde, as explained in the CLH report (page 82).

Concerning the disagreement about the wording on page 82 it is noted that the purpose of the terms "non-persistent metabolite" and "persistent metabolite" here was to differentiate the metabolites according to their occurrence under the conditions of the test. Intermediates which were present in ≥ 10% of the active substance throughout the experiment were referred to as "persistent" and the intermediate present in <10% was referred to as "non-persistent". Therefore, the dossier submitter would like to clarify that, on page 81 of the CLH report, in the second and third full paragraphs of page 82, and on page 90, the terms "persistent" and "non-persistent" do not refer to the persistence assessment required in the context of PBT assessment. Instead of the terms "persistent"

and "non-persistent" different wordings could have been used e.g. "persistent/non-persistent under the conditions of the test".
Alternatively, the definitions used in ECHAs guidance for biocidal products regulation (i.e., major metabolite, minor metabolite) could have been used, in which case each of the three identified metabolites would be regarded as "major metabolites" as they fulfil the criterion "formed in amounts of ≥ 10% of the active substance at any time of the degradation studies under consideration" (Guidance on regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products (BPR) (Version 1.0 July 2013); http://echa.europa.eu/documents/10162/15623299/biocides_guidance_information_requirements_en.pdf, page 24).

The purpose of adding Table 33 (and the footnotes) was to tentatively evaluate the environmental hazard classification of the metabolites identified in the anaerobic test, based on the information available. It is noted that the term "not persistent" as used after the subtitle "Characterisation of the metabolites observed in anaerobic water/sediment test" on pages 82 and 83 refers to persistence screening criteria in ECHAs guidance document R.11 which is referred to in the footnote "d" of Table 33.

Concerning Table 33, under the column titled "Occurrence in the anaerobic water/sediment test (US EPA Pesticide Assess-ment N 162-3)","persistent metabolite" refers to metabolites which were present in ≥ 10% of the applied radioactivity throughout the experiment whereas the metabolite which exceeded >10% of the applied radioactivity only on day 1 of the experiment is referred to as "intermediate metabolite".

Comment on omitted studies

Three acute fish studies, two acute studies on aquatic invertebrates (*Daphnia*) and one algae study available in the BPD review were omitted from the CLH dossier. In those tests the results are based on nominal concentrations and no evidence is presented that the concentrations have remained at least 80% from the nominal concentrations throughout the test. Glutaraldehyde is known to be readily biodegradable and relatively reactive and the available aquatic toxicity studies with measured concentrations show that glutaraldehyde in test water does usually not remain in the range of 80 to 120 % of nominal. Therefore, as already discussed in the CLH proposal (p. 92), studies without any analytical monitoring of the test substance concentrations were considered as unreliable and were not used for this CLH proposal.

In addition, there was one chronic study on *Ceriodaphnia dubia* which was not presented in the CLH proposal. According to BPD robust study summary the study was conducted under semi-static conditions and concentrations were measured before and after solution renewal. Nominal or measured concentrations were not provided and no information was given on concentrations during the study. The test results were mentioned to be based on 24-h weighted average concentrations but calculations were not presented. Since the reliability of the test could not be assessed due to poor documentation, the study was not used for CLH proposal.

RAC's response

1. Classification: RAC agrees with the classification based on fish, Daphnia and algae, as well as the new *Acartia tonsa* tests results. RAC emphasizes that the M-factor derived from the results is M=1 (0.1 < LC50 ≤ 1 mg/l).
2. General comments:
2.1. According to the opinion of RAC the wording of "persistent" and "not persistent" should be changed to "stable" and "not stable" during testing" (RAC advice).

2.2. Rap. finds information on the metabolites and the content of Table 33 important for the exclusion of anaerobic metabolites from classification, in spite of their presence in >10%. Their environmental fate and behaviour cannot be estimated without having the information, summarized in Table 33. RAP does not do not agree with the removal of Table 33 and the footnotes, as recommended by the comment.
2.3. The interpretation of the characteristic results of the metabolites can be upgraded by explaining that the stable metabolites (1,5-pentanediol and Compound A) are not bioaccumulative, are readily biodegradable under aerobic conditions, are not toxic and are strongly sorbed (chemisorbed) in the sediment – based on the information of registered substances in ECHA database (1,5-pentanediol) and QSAR estimations (Compound A). The metabolite with decreasing concentration under test conditions (5-hydroxy-pentanal) is included in the European Chemical Agency's C&L Inventory: not classified for environmental hazard due to the lack of data, but QSAR estimations confirm "no classification for environmental hazard".
Opinion of RAC is, that mentioning the contents of ECHA database and existing QSAR estimates as references does not mean any "suggestion" from DS.
2.4. The suggestion of BASF SE to amend the conclusion on p. 90 as follows: "*.....therefore glutaraldehyde will be removed in the environment*" is questionable, because the wording is not clear: where is glutaraldehyde removed from and where is it moved to?
2.5. RAC agrees with the exclusion of the studies of not sufficient quality. RAP's opinion is, that the selection of the key studies by DS is correct; studies without any analytical monitoring of test substances' concentrations were considered as invalid and were not used for the report.

Date	Country	Organisation	Type of Organisation	Comment number
08.11.2013	Belgium		MemberState	27

Comment received

Based on the results of the aquatic toxicity test on the most sensitive species (invertebrates: the marine copepod Acartia Tonsa with 48hEC50 = 0.07mg/l (geom.mean meas); Algae: Scenedesmus subspicatuswith 72hNOErC= 0.025mg/l (nominal)) the fact that the substance is considered as rapidly degradable it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Acute 1, H400 and Aquatic chronic 2,H411. Furthermore, the substance shows low potential to bioaccumulate.

In view of the proposed classification and toxicity band for acute toxicity between 0.01and 0.1 mg/l, an M-factor for acute toxicity of 10 could be assigned.

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Glutaraldehyde should be classified as N, R50 with SCL : N, R50 : C≥2.5%.

In conclusion : we agree with the proposed environmental classification by the Finish CA.

Dossier Submitter's Response

Thank you for your comments. However, the dossier submitter has revised the proposed environmental hazard classification due to new information received during the public consultation period. Please, see our response to the comment number 26.

RAC's response

The comment is outdated due to rejecting old and including new marine test results instead. DSD classification is not relevant any more.

Date	Country	Organisation	Type of Organisation	Comment number

05.11.2013	Germany		MemberState	28
Comment received				
p. 93, table 36/p. 99/p. 100/p. 101, table 40: According to Doc IIA of the glutaraldehyde CAR, the NOEC of the key study for the long-term toxicity to invertebrates of glutaraldehyde is 0.12 mg a.s./L. This value is mentioned on p. 99 as well. However, on p. 100 and in table 36 on p. 93 it is stated that the NOEC of the key study is 0.26 mg a.s./L and in table 40 on p. 101 the NOEC of 0.13 mg a.s./L is given. Please amend. p. 99: Please clarify whether the used test organism in the second test on the long-term toxicity to invertebrates is Ceriodaphnia dubia (as stated on p. 99) or Daphnia magna (as stated on p. 100 and p. 101 table 40).				
Dossier Submitter's Response				
Thank you for your comments. We apologise for the confusion. The correct NOEC of the long term toxicity study to aquatic invertebrates (*Daphnia*) is 0.26 mg/l. This value is based on arithmetic mean concentrations and chosen according to the instructions in the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances; " for flow-through test, where the concentrations do not remain within 80-120% of nominal, the effects concentrations should be determined and expressed relative to the arithmetic mean concentrations". The NOEC value of 0.12 mg a.s./l is based on time weighted average concentrations. The NOEC value of 0.13 mg a.s./l is based on geometric mean concentrations. Our intention was to use only the NOEC value based on arithmetic mean concentrations in the CLH dossier, however, unfortunately also other values were reported. Two valid long term toxicity tests to aquatic invertebrates were available and both of them were conducted with *Daphnia magna*. The study with *Ceriodaphnia dubia* was omitted from the CLH dossier due to poor documentation and the text should have been corrected accordingly (Please, see also our response to the comment number 26).				
RAC's response				
Thanks for the comment. The wording of the report needs complete harmonization after omitting not sufficient and including new studies.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2013	Sweden		MemberState	29
Comment received				
Hazardous to the aquatic environment: The Swedish CA supports the environmental classification of Glutaraldehyde (CAS 111-30-8) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiation. According to CLP criteria, glutaraldehyde is readily/rapidly degradable in the environment, based on ready biodegradation test with DOC removal of 70% is reached fulfilling the 10-day window criteria. Glutaraldehydes measured log Kow values=-0.80 to -0.36 which is below the CLP classification criteria for bioaccumulation: Log Kow < 4 and thus glutaraldehyde has no tendency to bioaccumulate. Glutaraldehyde fulfills the criteria for the classification H400 (L(E)C50 ≤ 1 mg/l)according to Regulation EC 1272/2008 (CLP) since the aquatic toxicity test with the marine crustacea				

Acartia tonsa EC50 = 0.07 mg/L. A M-factor of 10 is applicable based on 0.01 < L(E)C50 ≤ 0.1 mg/l.

The aquatic chronic toxicity of glutaraldehyde on the algae Scenedesmus subspicatus showed a NOECr (72 h) = 0.025 mg/l and on the algae Skelatonema costatum NOEC(72 h) =0.071 mg/l which leads to aquatic chronic 2, H411 classification based on 0.01 <NOEC ≤0.1 mg/l according to CLP.

Some specific comments that would have improved the discussion and justification for the environmental classification in the dossier:

- In section 2.2 "Short summary of the scientific justification for the CLH proposal": Specify which species and endpoint (LC50 or EC50) the classification of aquatic acute and chronic toxicity is based on. It would also have been helpful if this section had specified what criteria were used to conclude on the degradability.

- In section 5.1 Degradation, Table 23 "Summary of relevant information": To help the reader to understand on what ground the conclusion "Readily biodegradable" was reached specify what kind of degradation tests that were used and also the relevant degradation time (e.g. DT50, or DT 90) and % degradation.

Minor comment:
In section 5.4.2 Aquatic invertebrates, Table 39 Acute toxicity to invertebrates and Table 42 Comparison of glutaraldehyde data with criteria for environmental hazards: add 'Marine crustacean' prior to the name Acarcia tonsa.

Dossier Submitter's Response

Thank you for your comments and support. However, the dossier submitter has revised the proposed environmental classification due to new information received during the public consultation period. Please, see our response to the comment number 26.

Concerning comments to section 2.2. We agree that the conclusion on degradability could be more specified in this section also. However, this information is available elsewhere (in Sections 5.1.2.2., 5.1.3, and 5.5. (Table 42).

Concerning comments to Table 23 the guideline references, degradation percentages, test durations and other information concerning the ready biodegradability tests are available in Table 24. However, DT50 or DT 90 for ready biodegradability tests are not included (DT50 or DT 90 were not calculated for ready biodegradability tests as these values were not needed for classification purpose).

Concerning the comment to section 5.4.2 Aquatic invertebrates Table 39 and Table 42 and adding 'Marine crustacean' prior to name *Acartia tonsa*, the CHL Report is a proposal from the dossier submitter and, according to current RAC procedure, cannot be changed at this stage of the process.

RAC's response

The comment on M=10 is outdated.
In general RAC found the information mentioned by DS satisfactory for classification. Nevertheless some additional interpretation and comments, as well to find the best placing of the information can be considered by the DS. Also the results of the new *Acartia tonsa* acute toxicity results should be included instead of the old, omitted study results, for example in paragraph 5.4.2.1 on page 96, 5.5. on p. 103; in Table 39 and 42, as well as in the conclusion on p. 105 where still the former, already omitted and substituted *A. tonsa* results are listed. The inclusion of the new study into the reference list is also necessary.

ATTACHMENTS RECEIVED:

1. **Industry comments on the Proposed Harmonized Classification of Glutaraldehyde** *[Attachment 1],* submitted by Dow Benelux B.V. and BASF SE on 08.11.2013
2. **Additional BASF comments to the Proposal for Harmonised Classification and Labelling on: Glutaraldehyde** *[Attachment 2], submitted by a company-manufacturer on 11.11.2013*
3. ***Section A7.4.1.2_06 Acute toxicity to invertebrates (non-confidential version)*** *[Attachment 3],* submitted by Dow Benelux B.V. and BASF SE

CONFIDENTIAL ATTACHMENTS:

1. ***Section A7.4.1.2_06 Acute toxicity to invertebrates*** *[Attachment 4],* submitted by Dow Benelux B.V. and BASF SE on 08.11.2013