Additional BASF comments to the Proposal for Harmonised Classification and Labelling on:

Substance Name:	**Glutaraldehyde**
EC Number:	**203-856-5**
CAS Number:	**111-30-8**
Index Number:	**605-022-00-X**

Draft CLH dossier based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 (Dossier submitter: Finnish Competent Authority)

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 BASFSE is in line with the biocides registrants (BASF SE + Dow) but sees the need to provide additional information and arguments in this matter.

1) 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).

2) 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.

3) 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.

4) 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.

5) 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 <u>no</u> mutagenic hazard of glutaraldehyde for humans is to be expected.

21.06.2012

Industry comments to the RMS regarding the new classification proposal on Glutaraldehyde

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)

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.

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).