Industry comments on the Proposed Harmonized Classification of Glutaraldehyde

Introduction

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 M factor of 10 for the acute aquatic toxicity is no longer applicable.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

Specific comment on proposed Human Health classification changes

1) 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.

2) 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.

3) 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.

4) 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.

Specific comment on proposed Environmental classification changes

1) Proposed acute environmental classification and M factor

A new acute study on *Acartia tonsa* was conducted resulting in a LC_{50} 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 E_rC_{50} of 0.6 mg/L. Therefore, no M-factor has to be applied for acute toxicity of glutaraldehyde.

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.

References

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