

Helsinki, 24 June 2020

Note for the attention of Dr Tim Bowmer, Chairman of the Committee for Risk Assessment

Ref: Request to the Committee for Risk Assessment to review new information on acute toxicity by inhalation in relation to the harmonised classification of the substance EGBE

The Committee for Risk Assessment (RAC) is requested to review classification for acute toxicity by the inhalation route as adopted by RAC in its opinion of 14 September 2018 on EGBE.

1. Background

On 14 September 2018, RAC adopted an opinion on the harmonised classification and labelling of 2-butoxyethanol (ethylene glycol monobutyl ether (EGBE); EC Number: 203-905-0).

The dossier submitter (Germany) had proposed a classification for oral acute toxicity Cat. 4, dermal acute toxicity Cat. 3, and acute toxicity by inhalation Cat. 3. The RAC opinion concluded that 2-butoxyethanol should be classified for oral acute toxicity Cat. 4 and acute toxicity by inhalation Cat. 3, but not classified for dermal acute toxicity.

Following adoption and publication of the RAC opinion, manufacturers of the substance provided information on the acute toxicity of EGBE via the inhalation route additional to the information used by RAC to arrive at its conclusion. This information comprised a study report from a new GLP-compliant acute toxicity inhalation study conducted according to OECD TG 433 (adapted), which was made available after the RAC opinion had been published as well as the study report from another study in guinea pigs, rabbits and dogs, which had been previously submitted in the context of the consultation on the CLH report. The latter study is briefly acknowledged in the CLH opinion (under the heading "Comments received during public consultation"), but the results were not further mentioned in the RAC opinion in the assessment and conclusions on acute toxicity.

The availability of an additional guinea pig study by the inhalation route, which shows no treatment-related mortalities at achievable vapour concentrations, appears relevant for the assessment of acute toxicity. The Commission has noted that for the RAC conclusions on acute toxicity by other routes of exposure, RAC has acknowledged that the guinea pig appears to have a sensitivity to the leading toxic effect (haemolysis mediated through the metabolite butoxy acetic acid) which is similar to that of humans.

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The Commission has also noted the following:

- For oral acute toxicity, where LD₅₀ values from all tested species lay within the classification criteria for Cat. 4, the Acute toxicity estimate (ATE) for the classification of mixtures that RAC established was not based on the lower LD₅₀ values from studies in rabbits, rats or mice, but on the oral LD₅₀ (1200 mg/kg) from guinea pig studies, 'to ensure relevance for human hazard assessment', according to the RAC opinion.
- For the dermal route, RAC again considered the guinea pig data the most relevant, and did not use significantly lower dermal LD₅₀ values from rabbit studies to conclude on classification. In the RAC opinion it is stated that 'Since rabbits are reportedly more sensitive than humans to the acute toxicity of 2-butoxyethanol, the LD₅₀ in this species is less relevant for classification compared to Guinea pig data'. RAC also dismissed an old, not GLP or guideline-compliant guinea pig study that was the only one showing effects within the classification limit, and decided that classification is not warranted for that route.
- For the inhalation route, the initial assessment by the dossier submitter was based on two studies in guinea pig, in addition to studies in other species. For its final assessment, RAC used only one of the guinea pig studies (in addition to the studies in the other species). That guinea pig study dates from 1943, and only information from a secondary source was available. For this study, the LC₅₀ was above the saturated vapour concentration, and RAC acknowledged that exposure in this case was probably to a mix of vapour and mist. The other available GLP-compliant guinea pig study from 1994 – not considered in RAC's assessment - did not show mortality, but used a shorter exposure period of only one hour. In the RAC opinion it is stated that 'the data on Guinea pigs alone are borderline between classification and no classification for acute inhalation toxicity. [...], due to this situation RAC took all available studies in rats, mice and guinea pigs into account [...]'. This indicates that the uncertainty about the guinea pig data led RAC to take the available studies in the CLH report from all species into account to arrive at the conclusion that EGBE should be classified as Acute Tox. 3 with an ATE of 3.0 mg/L.

Given the high relevance given to guinea pig data in the assessment of acute toxicity via other routes of exposure and the lower value assigned to test data in other species with significantly lower LD₅₀ values; given the lack of clarity on whether all data available (including data provided during the consultation) was taken into account by RAC when concluding on the classification for acute toxicity by inhalation, and given the availability of new, GLP-compliant, acute inhalation test data in guinea pigs, a re-evaluation of acute toxicity by inhalation, taking into account the studies available in the original CLH report as well as the additional studies (existing and new) provided with this mandate is considered warranted.

2. Terms of Reference

In this re-evaluation, the Commission services would appreciate the consideration of the following aspects:

- A complete overview of all studies on acute inhalation toxicity available from the original CLH dossier, the public consultation and the submission accompanying this mandate, with an indication for each study to which extent it was taken into account in the RAC opinion.

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- Explanations on the relevance to humans assigned to individual studies and information on toxicity in different species.
- Where a specific study is not taken into account for the RAC conclusion, an explanation as to the reason why.

In accordance with Article 77(3)(c) of REACH, RAC is requested to review the available information on acute toxicity by inhalation, taking into account the abovementioned aspects, and, if appropriate, to amend the opinion of 14 September 2018 in relation to the classification for acute toxicity by the inhalation route and/or the setting of an ATE for the classification of mixtures.

3. Timescale for the RAC opinion

Considering the scope of the request, it is considered that the opinion be prepared in a shorter time than usually required for an opinion on harmonised classification. The Commission has also requested ECHA to conduct a consultation, for which the duration could be reduced compared to normal harmonised classification-related consultations given the limited amount of information that is new compared to the information considered in the original CLH dossier.

Within 12 months after the receipt of this request, ECHA should finalise the analysis with a view to confirming or amending the opinion of 14 September 2018 in relation to the classification of 2-butoxyethanol for acute toxicity by inhalation and/or the setting of an ATE for the classification of mixtures.

4. Remuneration

The task for RAC following from this request is not considered to fulfil any of the requirements of a transfer of funds to the competent authorities of the Member States pursuant to Article 14(1) of Regulation (EC) 340/2008 and therefore no remuneration will be paid by the Agency.

*(e-signed)*¹

Jukka Malm
Deputy Executive Director

Cc: Christel Musset, Peter van der Zandt

¹ As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.