Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling at EU level of

glyoxylic acid ... %

EC Number: 206-058-5
CAS Number: 298-12-4

CLH-O-0000001412-86-204/F

Adopted

8 June 2018

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CLH-O-0000001412-86-204/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: glyoxylic acid ...%

EC Number: 206-058-5

CAS Number: 298-12-4

The proposal was submitted by Germany and received by RAC on 8 May 2017.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at *http://echa.europa.eu/harmonised-classification-and-labelling-consultation/* on 19 July 2017. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 4 September 2017.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Nathalie PRINTEMPS

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on 8 June 2018 by consensus.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	Glyoxylic acid …%	206-058-5	298-12-4	Eye Dam. 1 Skin Sens. 1B	H318 H317	GHS05 GHS07 Dgr	H318 H317			B
RAC opinion	TBD	Glyoxylic acid …%	206-058-5	298-12-4	Eye Dam. 1 Skin Sens. 1B	H318 H317	GHS05 GHS07 Dgr	H318 H317			B
Resulting Annex VI entry if agreed by COM	TBD	Glyoxylic acid …%	206-058-5	298-12-4	Eye Dam. 1 Skin Sens. 1B	H318 H317	GHS05 GHS07 Dgr	H318 H317			B

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Glyoxylic acid has no existing Annex VI entry to CLP. The proposal from the Dossier Submitter (DS) only addressed the endpoints eye irritation/damage, skin corrosion/irritation and skin sensitisation.

The substance glyoxylic acid is supplied in the form of an aqueous solution at 50 % (v/v) according to the REACH registration dossier. All studies reported by the DS in the CLH dossier were performed on the 50 % glyoxylic acid solution.

The DS also proposed to include a Note B as glyoxylic acid may be placed on the market in aqueous solutions at various concentrations and, therefore, these solutions require different classification and labelling since the hazard could vary at different concentrations. RAC supports the inclusion of a Note B.

RAC notes that glyoxylic acid monohydrate (CAS 563-96-2; EC 679-230-4) and its salts exist in a higher concentration than 50 %. Glyoxylic acid monohydrate is self-classified for more severe hazardous properties than glyoxylic acid i.e. as Skin Sens. 1, Eye Dam. 1, Skin Corr. 1B, Resp. Sens. 1, Met. Corr. 1. Therefore, higher concentrations of glyoxylic acid (> 50 % v/v) may lead to more severe effects (e.g. skin irritation/corrosion) but RAC had no data with which to define any cut-off value for a higher sub-classification.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS proposed not to classify glyoxylic acid for skin corrosion/irritation potential based on a GLP *in vivo* rabbit study following OECD TG 404. In this study, erythema was observed in one out of 6 animals after 4h exposure of glyoxylic acid (50 % v/v aqueous solution) under semi-occlusive conditions (Guillot, 1984a). The slight erythema was fully reversible after 48 h. No other skin irritating effects were observed during the whole study period (72 h observation period only). The DS concluded that according to the CLP criteria, no classification should be applied.

Comments received during public consultation

One Member State Competent Authority (MSCA) questioned the validity and reliability of the *in vivo* study from Guillot (1984a). Indeed, the MS noted that glyoxylic acid (50 % v/v) has a very acidic pH (< 1), induced severe eye damage in an *in vivo* test guideline study and irritation in the preliminary skin sensitisation study.

The DS responded that significant irritating/corrosive effects on the skin would be expected based on the low pH value of glyoxylic acid (50 % v/v). Nevertheless, as the results of the *in vivo* study from Guillot (1984a) are considered reliable without restriction by the DS, the criteria to classify glyoxylic acid for skin corrosion/irritation are not met.

Assessment and comparison with the classification criteria

In a single skin irritation study OECD TG 404, glyoxylic acid (50 % v/v, aqueous solution) was applied to the intact skin of six rabbits. RAC considers the study reliable with limitations. Indeed, potential washing shortly after skin exposure was not reported. Moreover, the test material was applied on 2.5 cm^2 of skin instead of 6 cm^2 as recommended in the test guideline. Nevertheless, in the study, except a slight erythema score of 1 at 24 h (everage score of 0.33 for the period 24-72 h) in one out of 6 animals, reversible within 48 h, no other skin reactions were observed. Thus, glyoxylic acid does not meet the criteria for classification as skin irritant based on this study.

Irritation observed in the skin sensitisation studies should be used with care for assessing irritation potential (Guidance on the application of the CLP criteria, v. 5, July 2017; page 282). In the LLNA study performed in mice (Anderson *et al*., 2008), the use of acetone as a vehicle could have significantly enhance the penetration of the test material. In the guinea-pigs sensitisation test (Hoechst, 1975), necrosis observed after induction exposure could have been caused by intradermal injection with adjuvant. Therefore, RAC does not retain these studies to assess the irritation potential of the substance.

RAC notes as supportive information that no irritation potential was seen in an acute dermal toxicity study in rats (OECD TG 402), performed with glyoxylic acid 50 % v/v, aqueous solution (REACH registration dossier disseminated on ECHA website).

Glyoxylic acid in form of 50 % v/v aqueous solution has a reported pH of 0.3. According to the CLP criteria, extreme pH is expected to produce corrosive effects on the skin. Nevertheless, RAC consideres that existing reliable animal data should be given more weight than extreme pH in solution. Therefore, RAC concludes, in agreement with the DS proposal, that based on the standard *in vivo* rabbit study no classification for skin corrosion/irritation is warranted for glyoxylic acid 50 % v/v aqueous solution.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

In an OECD TG 405 GLP study performed in 6 rabbits, glyoxylic acid (50 % aqueous solution) caused severe eye irritation in rabbits (Guillot, 1984b). The study is considered reliable without restriction by the DS. The mean score for 24-72 h in the six rabbits were: 3.83 (corneal opacity), 1.72 (iritis), 3.94 (conjunctivae chemosis) and 2.22 (conjunctivae erythema). Eyes of three rabbits were washed out 4 seconds after instillation and other 3 rabbits 30 seconds after instillation. Individual data are not reported. None of the eye effects were reversible after 7 days of observation.

The mean 24-72 h scores are shown in the table below:

		Mean (24-72 h)	Max. score	Reversibility after 7 days
Conjunctivae	Chemosis	3.94	4	No
	Redness	2.22	3	No
Iris	Iritis	1.78	2	No
Cornea	Opacity	3.83	4	No

Based on the available *in vivo* study in rabbits supported by the extreme pH of glyoxylic acid (50 % aqueous solution), classification of glyoxylic acid as Eye Dam. 1; H318 is proposed by the DS.

Comments received during public consultation

One MSCA supported the DS's proposal to classify glyoxylic acid Eye Dam. 1; H318 based on the severe and irreversible eye effects.

Assessment and comparison with the classification criteria

Glyoxylic acid was tested for eye irritation in a study with 6 rabbits. RAC considers the study reliable with limitation as the observation period was only 7 days instead of 21 days recommended in the test guideline and as individual scores were not available. Nevertheless, the limitations are not considered to have compromised the positive results observed in the study.

Although individual values were not reported, it is possible to estimate, based on this *in vivo* study, that in 5/6 animals a mean score (24-48 h) for corneal opacity of 4 was obtained, meeting the criteria for serious eye damage (Guidance on the application of the CLP criteria, version 5, July 2017 (section 3.3.2.3.2.2), in case of 6 rabbits).

In agreement with DS, RAC is in the opinion that glyoxylic acid should be classified as Eye Dam. 1; H318 "Causes serious eye damage".

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS summarised in the CLH report two *in vivo* studies on skin sensitisation properties of glyoxylic acid, a Local Lymph Node Assay (LLNA) in mice and a Freud's complete adjuvant test with open challenge in Guinea-pigs.

The LLNA was conducted with a protocol similar to OECD TG 429 (GLP status unknown). In this LLNA study, glyoxylic acid was found to be a skin sensitiser since stimulation indexes significantly above 3 were found at 10 %, 20 % and 40 % v/v concentrations (Anderson *et al*., 2008). With regards to sub-categorisation, the DS proposed a category 1B based on the EC_3 value of 5.05 % v/v calculated by Anderson *et al*. (2008). It is not specified in the publication if the dose levels were expressed for the 50% v/v glyoxylic acid or if they were recalculated for the 100 % v/v substance. The DS considered that even if the percentage were given for the 50 % v/v glyoxylic acid, which they did not assumed to be the case, the resulting EC_3 would be 2.525 %, still supporting sub-category 1B (EC_3 value > 2 %).

The results of the Anderson *et al*., (2008) study are summarised in the table below:

Concentrations (%)	SI	Mean ear swelling, 24 h post-final exposure
0	-	-
2.5	< control	Data not shown
5	2.5	Data not shown
10	10.7**	~18 %
20	20.3**	>25 %
40	23.9**	>25 %

** $p < 0.01$

In the second study, a non-guideline non-GLP Freund's complete adjuvant test, glyoxylic acid (50 % v/v) was found to be a skin sensitiser since a skin reaction was observed in 100 % of the

animals in the test group after challenge (Hoechst, 1975). The DS considered this study non reliable but supportive as positive results were observed the study.

Therefore, the DS proposed to classify glyoxylic acid as a Skin Sens. 1B; H317 without an SCL.

Comments received during public consultation

One MSCA agreed with the proposed classification Skin Sens. 1; H317. Nevertheless, the MSCA commented that data are insufficient for sub-categorisation because the actual test concentrations used in the LLNA study are unknown.

In answer, DS considered that the test concentration used in the LLNA study are known and justified. According to the DS, the criteria for sub-categorisation 1B are met.

Assessment and comparison with the classification criteria

RAC considers the LLNA study (Anderson *et al*., 2008) reliable with limitations and deviations from the OECD TG 429:

- no justification of the use of acetone as a vehicle;
- results at 1.25 % v/v were not reported in the publication;
- pre-screened test differs from OECD TG 429. Animals were only exposed during 3 days instead of 6. No erythema scores have been determined.

Nevertheless, the above limitations and deviations are not considered to interfere with the reliability of the study. In this LLNA study, the EC_3 value was calculated by interpolation to be 5.05 %. At concentrations of 20 % and 40 % v/v glyoxylic acid, ear swelling scores above 25 % were observed suggesting potential irritating effect. A phenotype analysis of the lymphocytes from draining lymph nodes following exposure to glyoxylic acid was performed and resulted in statistically significant dose-related increase in $B220^+$ cell population at all tested concentration (10, 20 and 40 % v/v). The correlation of immunophenotypic marker $B220^+$ with sensitisation potential in the LLNA supports a true positive result.

In a supportive Freund's complete adjuvant test with open challenge, glyoxylic acid was found to be a potent skin sensitiser in male guinea-pigs. The study does not follow an OECD test guideline and few details are reported on the test method. Thus, in line with the DS, the study is only considered as supportive by RAC.

With regards to sub-categorisation, based on the positive results from the LLNA test, the EC_3 value > 2 % meets the criteria with sub-category 1B.

RAC agrees with the DS that the setting of an SCL is not justified.

Therefore, RAC concludes that glyoxylic acid warrants classification as Skin Sens. 1B; H317.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).