Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

sodium N-(hydroxymethyl)glycinate; [formaldehyde released from sodium N-(hydroxymethyl)glycinate]

EC Number: 274-357-8
CAS Number: 70161-44-3

CLH-O-0000001412-86-231/F

Adopted

14 September 2018

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CLH-O-0000001412-86-231/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: **sodium N-(hydroxymethyl)glycinate; [formaldehyde released from sodium N-(hydroxymethyl)glycinate]**

EC Number: **274-357-8**

CAS Number: **70161-44-3**

The proposal was submitted by **Austria** and received by RAC on **18 July 2017.**

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

PROCESS FOR ADOPTION OF THE OPINION

Austria 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 **13 September 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **30 October 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Agnes Schulte**

Co-Rapporteur, appointed by RAC: **Michael Neumann**

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 **14 September 2018** by **a simple majority of all members present and having the right to vote**.

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	sodium N-(hydroxymethyl)glycinate; [formaldehyde released from sodium N-(hydroxymethyl)glycinate]	274-357-8	70161-44-3	Carc. 1B Muta. 2 Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H350 H341 H302 H315 H319 H317	GHS08 GHS07 Dgr	H350 H341 H315 H319 H317			8, 9
RAC opinion	TBD	sodium N-(hydroxymethyl)glycinate; [formaldehyde released from sodium N-(hydroxymethyl)glycinate]	274-357-8	70161-44-3	Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 4 STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H350 H341 H332 H302 H335 H315 H319 H317	GHS08 GHS07 Dgr	H350 H341 H332 H302 H335 H315 H319 H317		inhalation: ATE = 3.0 mg/L oral: ATE = 1050 mg/kg bw	8, 9
Resulting Annex VI entry if agreed by COM	TBD	sodium N-(hydroxymethyl)glycinate; [formaldehyde released from sodium N-(hydroxymethyl)glycinate]	274-357-8	70161-44-3	Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 4 STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H350 H341 H332 H302 H335 H315 H319 H317	GHS08 GHS07 Dgr	H350 H341 H332 H302 H335 H315 H319 H317		inhalation: ATE = 3.0 mg/L oral: ATE = 1050 mg/kg bw	8, 9

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

With regards to substances that act via the released formaldehyde or any other substance acting by similar circumstances, RAC highlights that the classification is based on the (intrinsic) hazardous properties from the substance as such or its hydrolysis product, other cleavage products or any other metabolites and follows the criteria given by the CLP Regulation. For sodium N-(hydroxymethyl)glycinate (SHMG), no read across or risk-based approach is used for classification. The hydrolysis product, formaldehyde, is understood as the active agent (mainly locally active).

The considerations summarised by the dossier submitter (DS) in section 4.10.3 (*Summary and discussion of carcinogenicity*) of the CLH report facilitates the general understanding of the classification proposal:

"The active substance as manufactured represents sodium hydroxymethyl glycinate (SHMG) as a 50% aqueous solution. It represents a reaction product of formaldehyde and glycine. When SHMG is diluted in water, SHMG hydrolyses to formaldehyde and glycine. The high pH in the 50% solution (pH=11) or in a more diluted 5% solution slows down hydrolysis and formaldehyde release. However, the hydrolysis study indicates that in unbuffered aqueous solutions of 10%, 1% and 0.25% SHMG the pH is between 10.7 and 11.7, but still about 18%, 40% and 66% were hydrolysed. Contact with biological media should lead to a reaction of formaldehyde with proteins and shift the equilibrium towards further formaldehyde release. Acidic pH (like in stomach) would further support fast hydrolysis, the DT_{50} was smaller than 1.4 hours at pH 4 and 7. Therefore, we may theoretically assume a rate of 100% final hydrolysis in biological media. Given the molecular weight of 127 g/mol for SHMG and 30 g/mol for formaldehyde (factor 4.23) a 50% SHMG solution corresponds to less than 12% (w/w) formaldehyde. In-use concentrations of SHMG are usually very low (0.05% to 0.25%). With such high dilution in water, SHMG hydrolyses fully to formaldehyde and glycine. Glycine is an amino acid, a natural cell component, a food ingredient and compared to formaldehyde of low biological reactivity. Therefore, it is considered that the toxicity of SHMG relates primarily to the toxicity of formaldehyde."

The DS proposed to theoretically assume a rate of 100% final hydrolysis in biological media.

During the public consultation, a number of Industry Associations contested the approach to consider the theoretical maximum release of formaldehyde, and proposed instead to use measured levels of 'free' formaldehyde in the solutions for classification.

The DS responded that measured values of free formaldehyde do not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reacting with the biological targets, shifting the equilibrium towards further formaldehyde release. The DS proposed to follow the previous RAC opinions on other formaldehyde releasers and to consider total formaldehyde release upon which to base classification.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Based on 4 studies on acute oral toxicity and 2 studies each on acute dermal and inhalation toxicity the DS proposed classification as oral acute toxicity category 4 (H302 - Harmful if swallowed) and no classification for the dermal and inhalation route.

The acute oral LD_{50} is 1100 mg/kg bw in rats for the pure SHMG excluding any water, which corresponds to 2200 mg/kg bw for the substance as manufactured, i.e. as a 50% aqueous solution.

The LC_{50} (4 h) in inhalation studies was > 2.3 mg/L for the pure (solid) SHMG powder excluding any water (~ 4.6 mg/L SHMG 50% solution) and estimated to be 6 mg/L aerosol from SHMG as manufactured (50% aqueous solution). The DS recognised that concentrations below 20 mg/L could lead to classification. In the CLH report the DS argued that no lethality was observed at 6 mg/L, no classification was suggested (however, see section below).

The acute dermal LD_{50} is > 2000 mg/kg, for the pure SHMG was tested as moistened powder, which corresponds to > 4000 mg/kg for SHMG as manufactured as aqueous solution. No classification was proposed by the DS considering that no lethality was observed at the top dose level and this level coincides with the upper value of the acute toxicity estimate for classification as dermal category 4.

Comments received during public consultation

One company/manufacturer commenter proposed classification as acute toxicity category 4 for the oral (H302 - Harmful if swallowed) and also for inhalation route (H332 - Harmful if inhaled). The proposal was mainly based on the studies testing the solid material.

In their response, the DS recommended RAC to consider the proposal by the company/manufacturer for acute inhalation category 4, recognising that the DS´s initial proposal, which relied on data for the dry powder only, may need correction.

Assessment and comparison with the classification criteria

RAC agrees with the DS' proposal that the classification as **oral acute toxicity category 4 (H302 - Harmful if swallowed)** is warranted with an **ATE (oral) value of 1050 mg/kg bw** for the pure SHMG is adequate.

The LC_{50} (4 h) in inhalation studies was > 2.3 mg/L for the pure (solid) SHMG powder excluding any water (corresponding to ~ 4.6 mg/L SHMG 50% solution) and estimated to be 6 mg/L (aerosol) from SHMG as manufactured (50% aqueous solution).

In the inhalation study on SHMG as 50% aqueous solution (Doc IIIA 6.1.3.01), the DS' statement that no lethality was observed contrasts with the study report which says that 10% mortality by day 2 was seen at 4.9 mg/L, 70% mortalities were seen at 5.92 mg/L before day 7 and at 6.91 mg/L within 24 hours.

More weight is given to the aerosol study in comparison to the inhalation study on solid material (Doc IIIA 6.1.3.01) that up to 2.3 mg/L solid material did not show mortalities. Particle size (MMAD) of the solid test substance was 7 µm ± GSD of 2.06 µm. The test material was milled to less than 4 µm. No information, however, on the resulting MMAD and GSD is given in the report.

The calculated corresponding concentration of 4.6 mg/L for a 50% aqueous solution (Table 4.2.3 of the CLH report) may be at the edge of lethality as the first mortalities in the aerosol study started to occur at 4.9 mg/L. Thus, the lack of mortality in the study on solid test material could be considered as consistent to the aerosol study.

Therefore, in contrast to the original DS proposal, RAC considers appropriate the classification as acute inhalation toxicity category 4 (LC_{50} > 1 and ≤ 5 mg/L for dust/mist) based on the estimated LC_{50} value of 6 mg/L from SHMG (50% aqueous solution). Exposure duration of 4.5 hours would, after correction to 4 h- values, not change the category, but leads to a corrected LC_{50} value of 6.75 mg/L that corresponds to ~3.3 mg/L for the pure substance. RAC agrees on 3.0 mg/L as ATE value.

In conclusion, RAC considers appropriate to add the classification as **acute inhalation toxicity category 4 (H332 - Harmful if inhaled)** with an **ATE (inhalation) value of 3.0 mg/L**.

RAC agreed with **no classification for dermal acute toxicity**. The LD_{50} > 2000 mg/kg bw of the moistened solid SHMG is above the limit concentration for category 4 (≤ 2000 mg/kg bw).

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

Respiratory tract irritation from inhalation exposure is to be expected. In the absence of specific data and the DS' proposal to classify for skin and eye irritation, no additional classification for STOT SE 3 was proposed by the DS.

Comments received during public consultation

One MSCA proposed to classify for respiratory tract irritation. In their argumentation, SHMG as manufactured corresponds to 12% maximal releasable formaldehyde which is within the respiratory tract irritation range of SLCs (STOT SE 3; H335: C ≥ 5%).

Assessment and comparison with the classification criteria

During the first 24 h after exposure to 4.9 mg/L SHMG aerosol, irregular respiration, gasping, rales and laboured respiration were observed (acute inhalation study, Doc IIIA 6.1.3.01). Clinical signs of respiratory tract irritation were not interpreted as exclusive indication of (sub-)lethality since the death rate at this dose was 10% and animals recovered by day 10. Based on these observed effects, RAC considers that classification as **STOT SE 3 (H335 - May cause respiratory irritation) is warranted** for SHMG.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

No study on the SHMG as the marketed (50% aqueous solution) is available. There are skin irritation test data in rabbits for the SHMG in dry form as well as in the form of a 0.5% and 5% aqueous solution, which showed weak (below classification) dermal irritation (cf. CLH report, Table 4.4.1.1_1 - Skin irritation).

The DS, in a weight of evidence approach, considered the theoretical hydrolysis rates, pH values of unbuffered aqueous solutions, as well as information from skin sensitisation studies in guinea pigs, and proposed classification for skin irritation, category 2, for SHMG as manufactured (50% w/w aqueous solution) as well as for SHMG 100%.

Comments received during public consultation

One Industry/trade association considered no classification for skin irritation as appropriate. They questioned the relevance of theoretical concentrations of formaldehyde after hydrolysis and relied their argumentation on the lack of significant irritation by SHMG from the available skin irritation tests, as well as the lack of irritation effects in the sensitising studies on guinea pigs. In a pilot study (Doc IIIA 6.1.5.0.2) on sensitisation, skin irritation was analysed after topical application with 25%, 50%, 75% and 100% concentration (in distilled water) (no data on exposure duration and conditions). No erythema and no oedema were observed.

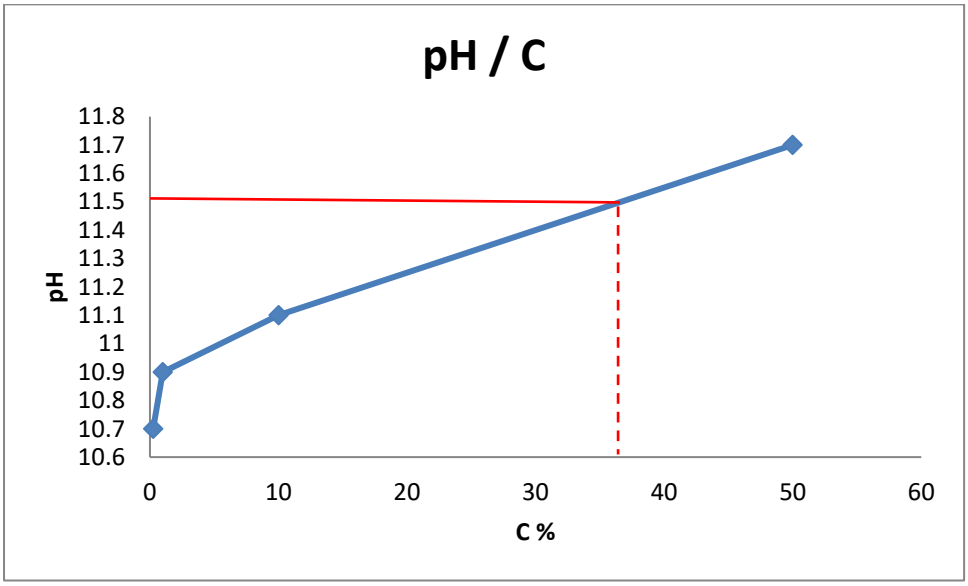
Assessment and comparison with the classification criteria

RAC notes the lack of skin irritation data for the SHMG as marketed (50% solution), and the lack or low-level effects from the dry/moistened powder, 0.5 and 5% solutions, which would not justify classification for skin irritation.

RAC acknowledges the theoretical considerations of the DS. Different lines of evidence need to be considered:

- The SHMG 5% aqueous solution showed weak irritative effects with scores below the mean value of 2.3 for the 24, 48, 72 hours after removal. RAC assumes SHMG as 50% aqueous solution to exert stronger irritative effects.
- Testing of dry material SHMG powder, not moistened or moistened, induced mild irritation (below classification criteria). RAC considers testing of dry material as less predictive for the human situation due to the non-sweating conditions of the rat skin.
- RAC notes the measured data revealing high pH values of ≥ 10.7 in un-buffered SHMG aqueous solutions of 0.25% and above (see hydrolysis study Doc IIIA 7.1.1.1.1., Table 2). The measured pHs were 10.7 (0.25%), 10.9 (1%), 11.1 (10%) and 11.7 (50% SHMG) (see figure below). RAC also notes the CLH report does not refer to the 50% solution.

Figure: pH values at different concentrations of SHMG aqueous solution



According to CLP Guidance 3.2.2.1.2.2., pH extreme values ≥ 11.5 are expected to produce significant effects on the skin and classification as a corrosive should be considered. The observed pH rises with the concentration of SHMG in aqueous solution and theoretically the value of 11.5 is expected to be exceeded at concentrations > 35%.

- The DS considered that 5% SHMG may theoretically hydrolyse at an assumed 100% hydrolysis rate to 1.2% formaldehyde. Formaldehyde is classified in CLP, Annex VI as Skin Corr. 1B, the general concentration limit for classification as skin irritant is ≥ 5% (5 % ≤ C < 25 %).

  The hydrolysis test revealed that SHMG will completely hydrolyse within short time (half-time could not be estimated for the non-buffered solution and was < 1.4 h for 0.25% and 1% buffered solutions at pH 4, 7, and 9). Following the assumption that the hydrolysis product formaldehyde is produced, 50% SHMG could at maximum produce formaldehyde concentrations of 12%. Based on the formaldehyde production, SHMG as a 50% aqueous solution should be classified as skin irritant.

- The DS did also take the information from a maximisation test (GPMT) into account (Doc IIIA 6.1.5.02). The dermally applied challenge dose (topically exposed during 24 hours) of 50% aqueous solution of SHMG produced very slight to grade 4 erythema indicative of the sensitising potential. Erythema is here considered as the response of senstising properties of the previously interdermally applied SHMG. The available information in guinea pigs on the range of grades for the erythema is not robust to assess skin irritation properties, as this study type is not accepted for the endpoint skin corrosivity/irritation. However, it should be noted (as supplementary information) that no corrosive effects were noted at challenge concentrations up to 50%. Skin irritation was not seen in a pilot study (to estimate the irritative concentration) with 24%, 50%, 75% and 100% aqueous concentrations. However, the study design (no data on exposure duration) and reporting is insufficient compared with standard studies on skin irritation.
  Another Guinea pig (Buehler) study (Doc IIIA 6.1.5.01) was considered less informative since the test substance was the moistened powder.
  In general, CLP guidance questions the relevance of Guinea pigs to predict the irritative properties due to the low sensitivity of Guinea pigs (Guinea pigs < rats < rabbits).

Considering the available data, the elements of evidence and that no clear indication of corrosivity was observed in the eye irritation tests, RAC regards the pH-values alone insufficiently convincing to conclude on the corrosivity of SHMG. RAC, however, takes into consideration that high pH values may be generated at higher SHMG concentrations and may contribute to the irritating effects of SHMG.

In a weight of evidence approach, taking into consideration the mild irritation observed with a SHMG 5% aqueous solution, the lack of data for SHMG 50% aqueous solution, for which the irritative effect is expected to be stronger and likely to fulfil the classification criteria, the concern from the hydrolysis product formaldehyde (classified as a corrosive) and the high pH values in un-buffered SHMG solutions, RAC agrees with the DS proposal to classify **SHMG** as **skin irritation 2 (H315 - Causes skin irritation)**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS presented eye irritation data for SHMG in the dry form (powder) and as a 5% and 50% aqueous solution (cf. CLH report, Table 4.4.2.1_1 - Eye irritation) and suggested classification for eye irritation category 2.

While no eye irritation was observed in one rabbit eye irritation test with a 5% SHMG solution (all scores were 0, Doc IIIA 6.1.4/09) that test was considered as not reliable due to a very scarce method description. In another rabbit eye irritation test with a 5% SHMG solution (Doc IIIA 6.1.4/11), conjunctiva redness score of 2 in 2/6 animals were observed, which was considered borderline with regard to the classification criteria (≥2/3 animals) . In the rabbit eye irritation study with SHMG as manufactured (50% aqueous solution, Doc IIIA 6.1.4/12) the conjunctiva redness score was ≥ 2 in 2/6 animals and the redness conjunctiva average (24/48/72 hour) score was 1.4. All other endpoints were below the criteria and all irritations cleared by day 10. Considering that the criteria for classification are a conjunctiva redness score of ≥ 2 for at least 2/3 animals, the results from this test were considered by the DS as indicative of irritating effects which may be sufficient for classification.

In the test with SHMG powder (Doc IIIA 6.1.4/08), the average scores for conjunctive redness and chemosis, for the 6 animals tested, were ≥ 2 and reversible by day 14, which support the eye irritation category 2 classification.

Comments received during public consultation

One company/manufacturer commenter supported eye irritation category 2 based on the available studies. One MSCA also supported this classification.

Assessment and comparison with the classification criteria

For the observed effects (conjunctival erythema (redness) and conjunctival oedema (chemosis) the CLP guidance 3.3.2.3.2.2 indicates in case of 6 rabbits tested, classification for eye irritation category 2 applies if at least 4 out of 6 rabbits show a mean score per animal of ≥ 2. In tests on SHMG 50% aqueous solution mean scores of ≥ 2 for redness were reported in 2 out of 6 animals. These findings alone would not justify classification.

The study report (Doc IIIA 6.1.4/12) indicates that 6 rabbits eyes remained unwashed, 3 rabbits eyes were flushed for one minute with water 20-30 seconds after instillation of test material. No effects in any of the animals were observed on cornea and iris. The sum of the mean scores for conjunctiva effects were 9.7 after 1 hour, 9.0 after 24 h, 5.0 after 48 h, 3.5 after 72 h and effects were cleared by day 10.

The information given in the evaluation by RMS was that the average (24/48/72 hour) scores for redness ≥ 2 was seen in 2 (non-rinsed) animals, all other were < 2, while the average for chemosis for the same time points was 2 in one animal, for all other < 2. In this section, a copy of the original study report indicated the individual results for six (non-rinsed) animals. According to this table (6.1.4.12_1 in Doc IIIA 6.1.4/12), the 24/48/72 hour mean score was ≥ 2 for 2 but not for 4/6 animals as required by the CLP criteria. Solely from the results of this study, there would be no need for classification and DS considered the results as borderline for classification as eye irritant.

The testing of the SHMG powder (Doc IIIA 6.1.4/08) was conducted on 5 male and 4 female rabbits (cf. CLH report, Table 4.4.2.1_1) on 6 animals seems to be incorrect. The study summary

in the CAR documents says that six rabbits eyes (out of the total of 9 rabbits) remained unwashed, 3 rabbits eyes washed with 20 mL distilled water 30 seconds post dose (no data on sex distribution).

The results were reported as follow: in unwashed eyes, corneal opacity, noted in 6/6 eyes with mean score 2. However, on day 7, pannus (effect indicating corrosivity) were seen in 3 eyes. Iritis, noted in 6/6 eyes with mean score 1 in 5/6, cleared by day 7. Conjunctival irritation redness and chemosis, each with mean scores ≥ 2 were noted in 6/6 eyes. All effects were cleared by day 14. These observed effects support classification as Eye Irrit. 2, while the pannus lesion in 3 eyes at day 7 indicates a corrosive effect that, however, was reversible at day 14. In washed eyes, corneal capacity and iritis, noted in 2/3 eyes, cleared by day 7. Conjunctival irritation, noted in 3/3 eyes, cleared by day 14. All effects were reported to be cleared by day 14. The mean scores in washed eyes were lower than in unwashed eyes; based on the mean scores of cornea opacity of 2, SHMG powder could be considered irritant.

RAC is aware that testing of a powder may generate particle-related irritative effects that may contribute to the severity of the test substance-related effects. For solid SHMG , this type of contribution may be difficult to assess as hydrolysis after contact with the physiological tear fluid may occur and generate formaldehyde at the site of contact.

Formaldehyde is classified as skin corrosive category 1B (which labelling covers also eye corrosivity), and classification as eye irritant category 2 is required for concentrations ≥ 5% and < 25%.

The pannus effects observed in the study on SHMG powder appeared with delay on day 7 after treatment. Although it indicates abnormal fibrovascular/granulation tissue and is an indicator for corrosivity, it was reversible until day 14 of the observation time and thus was not sufficient for corrosivity classification.

Based on SHMG irritating properties as powder, which tests showed effects consistent with the CLP criteria for classification as eye irritant category 2, the evidence from mild irritation of SHMG 50% aqueous solution and the concern from the hydrolysis product formaldehyde (classified as corrosive) RAC agrees, in a weight of evidence approach, with the DS proposal to classificaty **SHMG as Eye Irrit. 2, (H319 - Causes serious eye irritation)**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Data from a human study with 102 individuals who received 9 topical applications of 0.5% SHMG solution neutralized to pH 7 within 3 weeks did not show any irritation or sensitising reaction at a previously untreated site after another challenge following a rest of 2 weeks. The applied concentration of 0.5% SHMG solution corresponds stoechiometrically to 0.12% formaldehyde which is below the (harmonised classification) concentration limit for formaldehyde of 0.2% (as skin sensitising category 1).

The DS presented the available animal (guinea pig) studies for SHMG (cf. CLH report, Table 4.6.1.1_1) and proposed the GPMT from 1984 (CAR IIIA 6.1/02) as the most reliable study. The other studies, including Buehler test from 1997, were considered not reliable due to the low number of animals (10 instead of standard 20 for the Buehler test) and the low and non-irritant doses employed.

In the 1984 GPMT, positive reactions were observed in animals after intradermal induction with SHMG 5% solution followed by a topical induction with moistened powder at day 8 and topical challenge concentrations of 50%, 5% and 0.5% SHMG followed (corresponding to 12%, 1.2% and 0.12% formaldehyde). Positive reactions were observed at 50% SHMG (first challenge on day 22) in 5/10 animals (24 h post removal) and 7/10 animals (48 h post removal). Potency differentiation to category 1A or 1B was not possible since no induction concentration lower than 5% was tested. SHMG (both pure and as manufactured, 50% solution) are proposed by the DS to be classified as skin sensitizer category 1.

The generic concentration limit of ≥1% for skin sensitizer category 1 corresponds to 0.24 % of formaldehyde as hydrolysis product. This is slightly above the specific concentration limit of 0.2% for formaldehyde. The DS found the difference between 0.85% SHMG (which corresponds to 0.2% formaldehyde) non-significant and proposed to apply the generic concentration limit of 1% for SHMG.

Comments received during public consultation

One company/manufacturer commenter disagreed with the DS' evaluation and found the negative Buehler test with moistened powder more reliable.

Assessment and comparison with the classification criteria

A sensitising potential was identified from the GPMT (CAR IIIA 6.1.5/02) with 70% and 40% positive animals at 50% and 5% challenge concentrations, respectively, following intradermal induction with a 5% concentration. Since no lower induction concentrations were tested, a discrimination between category 1A and 1B is not possible.

Based on the observation of ≥ 30 % positive reactions and the DS' considerations on the SCL, RAC agrees with the DS proposal to classify SHMG as **skin sensitizer category 1 (H317: May cause an allergic skin reaction) with no specific concentration limits**.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

An oral 28-day study on rats that received SHMG 5% w/v in water at doses of 0, 40, 160 and 640 mg/kg bw/d revealed adverse effects at the high dose level only. One unscheduled death in a female, lower protein levels, non-significantly lower mean haemoglobin and haematocrit values and subacute gastritis and ulceration of the glandular stomach in male and female animals were observed. Significantly lower body weight was seen on day 14 and 21 in male rats (≤ 8%). No adverse effects were observed in an oral 90-day study on rats that received received SHMG 2% w/v in water at doses of 0, 10, 40 and 160 mg/kg bw/d. Since no adverse effects that may justify classification for STOT RE (guidance value ≤100 mg/kg bw/d for category 2) in any of these studies, no classification was proposed.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

For information, 160 mg/kg bw/d SHMG as 2% aqueous solution corresponds to 38 mg/kg bw/d formaldehyde (no harmonised classification for STOT RE). **RAC concurred with the DS' proposal that no classification is needed**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The DS proposed to classify SHMG as mutagen category 2 based on the available positive *in vitro* genotoxic data and taking into account the classification of its hydrolysis product formaldehyde (mutagen category 2).

There are several positive *in vitro* tests for SHMG; a mouse lymphoma assay, chromosomal aberration tests with CHO cells and human lymphocytes. A bacterial gene mutation assay (Ames test) is ambiguous, and a UDS test is negative. These data lead to the conclusion that the substance induces mutagenic effects *in vitro*.

The available *in vivo* tests (bone marrow micronucleus in rat and mouse; UDS test) are negative. Regarding the relevance of the negative *in vivo* results, the DS argued that it seems to be likely that neither SHMG, nor its hydrolysis product formaldehyde reached the target tissues. Based on the available data and mechanistic consideration of formaldehyde release, local genotoxic effects are to be expected from SHMG.

The results of the *in vitro* and *in vivo* genotoxicity tests for SHMG and free formaldehyde are similar. Both substances are *in vitro* mutagens; within the standard animal tests for systemic genotoxicity both substances are negative. *In vivo* data for local genotoxicity are available only for formaldehyde, and are positive.

The DS proposed to base the classification of SHMG on the data of the hydrolysis product formaldehyde (classified as Category 2 mutagen) due to the consideration that formaldehyde release is dominating the toxicity of SHMG.

Comments received during public consultation

One MSCA supported the proposed classification as mutagen category 2 based on the hydrolysis product formaldehyde.

One industry representative is of the opinion that classification for mutagenicity is not justified.

Assessment and comparison with the classification criteria

The evaluation of the genotoxic data of SHMG by the DS and RAC does not differ. SHMG is an *in vitro* mutagen but induces no genotoxic effects *in vivo* in different target organs.

***In vitro* data**

SHMG induced with and without S9 mix gene mutations (mouse lymphoma assay: Lloyd, 2002) and clastogenic effects (chromosomal aberration test with CHO cells (Putman and Schnadly, 1992) and with human lymphocytes (Whitwell, 2002)) in mammalian cell cultures. A bacterial gene mutation test is equivocal (Haworth, 1983), while an UDS test with rat hepatocytes is negative(Stankowski, 1995).

***In vivo* data**

A rat bone marrow micronucleus test (ISP, 2002) and a mouse bone marrow micronucleus test (ISP, 1987) as well as a UDS test (ISP, 1994) were negative.

Due to its reactivity (hydrolysis to formaldehyde), a low systemic availability is expected for SHMG. Therefore, the induction of systemic genotoxic effects in standard animal tests is unlikely. However, a local genotoxic effect produced by the hydrolysis product formaldehyde is expected. Therefore, the read-across to formaldehyde, which has a harmonised classification as mutagen in category 2 due to the induction of local genotoxic effects, is justified.

It is assumed that SHMG has a low systemic availability due to its reactivity. Accordingly, the available *in vivo* results are of low relevance and do not allow the conclusion that the substance is not genotoxic in the whole animal. There is no test with SHMG which assessed whether genotoxic effects will be induced in cells at site of first contact. For the evaluation of toxicological properties of SHMG, the fact that its hydrolysis product formaldehyde is inducing local genotoxic effects and is already classified as Category 2 mutagen is taken into account. Based on positive *in vitro* data of SHMG and on read-across to formaldehyde, RAC agrees with the DS proposal to **classify SHMG as a Germ Cell Mutagen Category 2 (H341 – Suspected of causing genetic defects)**.

The classification proposal for SHMG is in line with previous decisions on formaldehyde and other formaldehyde releasers.

Some RAC members expressed their discomfort with the classification as in their view the criteria should only be interpreted as they specifically relate to germ cell mutagens. They expressed their disagreement on the classification as Muta Cat. 2 based on the local genotoxic effects in a minority position (see associated documents to this opinion).

RAC agreed with the DS proposal to apply Note 9 in line with the previous formaldehyde releaser opinions. **Note 9**: "*The classification as a mutagen need not apply if it can be shown that the maximum theoretical concentration of releasable formaldehyde, irrespective of the source, in the mixture as placed on the market is less than 1%.*"

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

There are no carcinogenicity studies on SHMG and the DS proposed to classify SHMB as a carcinogen 1B based on the hydrolysis product formaldehyde.

SHMG as manufactured is a 50% aqueous solution that hydrolyses to formaldehyde and glycine. The DS considered the toxicity of SHMG as related to the toxicity of formaldehyde; complete hydrolysis of a 50% aqueous solution of SHMG would correspond to 12% (w/w) formaldehyde. The DS noted that the formaldehyde releaser is difficult to characterize since it is instable with half-lives depending on dilution, temperature and pH.

The high pH, in the 50% solution (pH=11) or in a more diluted 5% solution, slows down the hydrolysis and the formaldehyde release. However, the hydrolysis study indicated that in unbuffered aqueous solutions of 10%, 1% and 0.25% the pH is between 10.7 and 11.7, but still about 18%, 40% and 66% were hydrolysed.

Contact with biological media should lead to a reaction of formaldehyde with proteins and shift the equilibrium towards further formaldehyde release.

In vitro genotoxicity data for SHMG was considered as supporting the assumption of local genotoxicity and consequently a local carcinogenicity.

The DS suggested adding note 8 (as agreed for other formaldehyde releasers) that solutions of formaldehyde releasers only need to be classified if the maximal releasable formaldehyde content is above 0.1%.

Following a wight of evidence evaluation and considering the conclusion of RAC on other formaldehyde releasers ("reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)" and "reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1)" and "4-(morpholin-4-ylmethyl)morpholine"), is the DS proposed to base classification of SHMG on the data of the hydrolysis product formaldehyde. For the same reason, the DS suggested to include a specific note 8: "The classification as a carcinogen need not apply if it can be shown that the maximum theoretical concentration of releasable formaldehyde, irrespective of the source, in the mixture as placed on the market is less than 0.1%."

Comments received during public consultation

Company/manufacturer and industry association commenters disagreed with the assessment of SHMB based on equivalency and read across to formaldehyde and argued that repeat dose toxicity study demonstrate the lack of neoplastic growth or aberrant tissue at the site of gavage.

One MACA supported the proposed classification as carcinogen category 1B.

Assessment and comparison with the classification criteria

Consistent with the classification of other formaldehyde releasers and in agreement with the DS proposal, RAC considers the classification of **SHMG as carcinogen category 1B (H350 - May cause cancer)** to be warranted.

RAC agreed with the DS proposal to apply Note 8 in line with the previous formaldehyde releaser opinions. **Note 8:** "*The classification as a carcinogen need not apply if it can be shown that the maximum theoretical concentration of releasable formaldehyde, irrespective of the source, in the mixture as placed on the market is less than 0.1%."*

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Fertility

No studies allowing to evaluate the SHMG toxicity toward fertility and sexual function are available. The toxicity of SHMG is considered to be related to the hydrolysis product formaldehyde.

In repeated dose studies, no adverse effects on the reproductive organs were recorded at the high dose levels. According to the DS, this provided a good indication that it is unlikely there will be an effect on fertility or sexual function following repeated administration of SHMG. Furthermore, it is not to be expected, that the breakdown product, formaldehyde, will reach the reproductive organs.

Developmental toxicity

The DS presented a developmental study (similar to OECD TG 414) on SHMG.

Female Sprague Dawley rats were dosed by gavage with the active ingredient at doses 0, 75, 150 and 225 mg/kg bw/d from day 6 through day 15 of gestation.SHMG was administered to the animals as a 5% w/v solution. Caesarean section was performed on each dam on day 20 and the uterus of each dam excised and weighed. No effects on numbers of corpora lutea, viable and non-viable foetuses, early and late resorptions, total number of implantations, and foetal and uterine weights were recorded. There were no significant differences observed in any of the end points examined except for maternal toxicity noted in the high dose group as evidenced by suppressed body weight gain and reduced food consumption. Foetuses were examined for evidence of variations and malformations. A significant increase of skeletal malformations was observed in the low dose group only: 4.4% vs. 0% in control. However, the malformation shaped scapula (broad and flat) and short appendicular bones (humerus, radius, ulna, femur, tibia and fibula), were present only in one litter and no dose response was observed.

Overall, a maternal NOAEL of 150 mg/kg bw/d was observed with the test substance applied as 5% aqueous solution. The developmental NOAEL was higher (225 mg/kg bw/d; Doc III A6.8.1).

In conclusion, the DS did not see evidence to classify for reproductive effects.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

RAC notes the lack of dose-related effects on the reproductive organs from repeated dose studies with SHMG (consistent with the results of the formaldehyde studies) and the lack of adverse effects on the development of offsprings from the available developmental toxicity study with SHMG.

No specific studies on fertility are available.

Based on the lack of data and the lack of indications from the available developmental study and repeated dose studies, RAC agrees with the DS that **no classification for reproductive toxicity for SHMG is warranted**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's (DS) proposal

Sodium N-(hydroxymethyl)glycinate (SHMG) is a reaction product of formaldehyde and glycine. When SHMG is diluted in water, it hydrolyses to formaldehyde and glycine. Glycine is an amino acid, a naturally occurring biological molecule, a food ingredient and compared to formaldehyde of low concern as a toxin. Therefore, the toxicity of SHMG relates primarily to the toxicity of SHMG and formaldehyde.

Degradation

The dossier submitter proposed to consider SHMG as rapidly degradable. The basis for this proposal is an OECD TG 301B test result (Doc III A 7.1.1.2.1_01, Study A 7.1.1.2.1). In the study, a predominantly domestic activated sludge served as inoculum (cf. Table 5.1.2.2-1) was used. Mean carbon dioxide evolution exceeded 60% of the theoretical CO_2 yield over the course

of the 28 day incubation, and the 10-day window was fulfilled. Mineralization of the test substance reached a maximum of 99% in this study, indicating that the active ingredient in sodium hydroxymethyl glycinate manufactured as aqueous solution was readily biodegradable. The validity criteria of the guideline were met; however the reporting was rather poor. In general, the documentation of the study was not complete (e.g. number and volumes of test vessels missing, descriptions of controls). Therefore, this study was rated as Klimisch 2. SHMG is also unstable to hydrolysis with hydrolysis values being below 1.4h at pHs 4, 7, and 9 (at 10, 25, and 40 °C).

Aquatic Bioaccumulation

The DS proposed that SHMG does not meet the CLP criteria for bioaccumulation. The basis for this proposal is a measured log K_{OW} value of -1.533 (cf. Doc III-A 3.9). However, the test substance will hydrolyse under the test conditions, especially at the applied concentration (10 µL in 10 mL ISA water), and thus the partition coefficient of the hydrolysis products has actually been measured. Calculations (KOWWIN v1.67) show a $logP_{ow}$ of -6.19 for the sodium salt and -3.41 for the non-ionized form.

There are no experimental BCF data available. Due to the hydrolysis properties of SHMG (cf. Doc III-A 7.1.1.1.1), experimental determination of the BCF is not possible (Doc III A7.4.2 – Justification). Overall, a low bioaccumulation potential is expected for SHMG.

Acute Toxicity

The dossier submitter proposed to not classify SHMG as acutely hazardous to the aquatic environment. The basis for this proposal was that from relevant and reliable tests for all three trophic levels, the lowest available acute $L(E)C_{50}$ values for SHMG are above 1 mg/L.

Fish	*Lepomis macrochirus*
Doc III A7.4.1.1/03: Wildlife International Ltd (1996), FIFRA Subdivision E, Series 72-1	96h-LC_{50} 75 mg/L for pure SHMG excluding water (calculated, based on mean measured concentrations of sodium glycinate)
Invertebrates	*Dapnia magna*
Doc III A7.4.1.2/02: Wildlife International Ltd (1996), FIFRA Subdivision E, Series 72-2 and ASTM Standard E729-88a	48h-EC_{50} 39 mg/L for pure SHMG excluding water (calculated, based on measured concentrations of sodium glycinate)
Algae	*Desmodesmus subspicatus*
Doc III A7.4.1.3/02: BMG Engineering Ltd (2015), OECD 201: Algal Inhibition Test	72h-ErC_{50} 11.76 mg/L for pure SHMG excluding water (calculated, based on measured concentrations of formaldehyde)

Hydrolysis products

Acute formaldehyde toxicity data are available in the REACH registration dossier, which is disseminated on ECHA's website. Summaries of these data are also presented in the background document (BD). Glycinate and its salts such as sodium glycinate are naturally occurring substances present in all life, they are therefore unlikely to be of concern. This is confirmed by the QSAR data for glycine and sodium glycinate (summarised in BD). The data for formaldehyde

and glycinate/sodium glycinate indicate acute toxicity values above 1 mg/L for all trophic levels, further indicating that no classification is warranted.

Chronic Toxicity

The dossier submitter proposed to not classify SHMG as chronically hazardous to the aquatic environment. The basis for this proposal is that for algae a reliable 72hr-NOE_rC is available which is above 1 mg/L. For fish and crustaceans, no chronic aquatic toxicity data are available. However, as SHMG is rapidly degradable and has a low potential for bioaccumulation, a conclusion of no classification is derived via the surrogate approach.

fish	no chronic aquatic toxicity data available
crustacean	no chronic aquatic toxicity data available
algae	*Desmodesmus subspicatus*
Doc III A7.4.1.3/02: BMG Engineering Ltd (2015), OECD 201: Algal Inhibition Test	72h-NOE_rC 2.5 mg/L for pure SHMG excluding water (calculated, based on mean measured concentrations of formaldehyde)

Hydrolysis Products

Chronic formaldehyde toxicity data are available in the REACH registration dossier, which is disseminated on ECHA's website. Summaries of these data are also presented in the background document (BD). The available chronic toxixity data for formaldehyde is a *Daphnia* 21 d NOEC of 1.04 mg/L, indicating no classification. No chronic data toxicity were available for formaldehyde in fish or algae. However, as formaldehyde appears to be both rapidly degradable (based on ready biodegradation of 99% after 28 d) and has a low potential for bioaccumulation (measured Log k_{ow} 0.35 and calculated BCF 0.396 L/kg), a conclusion of no classification is derived via the surrogate approach. As the QSAR derived chronic toxicity values for glycinate/sodium glycinate indicates toxicity above 1 mg/L for all trophic levels (summarised in BD), this further indicated that no classification for SHMG is warranted.

Comments received during public consultation

Two MSs commented and both agreed with the proposal to not classify SHMG as hazardous to the aquatic environment.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the dossier submitter to assess SHMG as being rapidly degradable, based on being readily biodegradable under OECD TG 301 B and unstable to hydrolysis.

Aquatic Bioaccumulation

RAC agrees with the dossier submitter that SHMG does not fulfil the criteria on aquatic bioaccumulation, based on a measured Log K_{ow} of -1.533 and being rapidly hydrolysed at environmentally relevant pHs and temperatures.

Acute Toxicity

RAC agrees with the dossier submitter **not to classify SHMG as acutely hazardous to the aquatic environment**, based on measured acute toxicity values above 1 mg/L for SHMG and formaldehyde, as well as QSAR data for glycine/sodium glycinate at all trophic levels.

Chronic Toxicity

One available 72 h NOE_rC for algae is above 1 mg/L. Long-term toxicity data for fish and invertebrates not available. However, as SHMG is rapidly degradable and has a low potential for bioaccumulation, the conclusion via the surrogate approach is no classification. Furthermore, a *Daphnia* NOEC for formaldehyde was above 1 mg/L. No chronic data toxicity are available for formaldehyde in fish or algae. However, as formaldehyde appears to be both rapidly degradable and has a low potential for bioaccumulation, no classification is derived via the surrogate approach. Furthermore, QSAR data for glycine and sodium glycinate show results considerably above 1 mg/L for all trophic levels. Overall, RAC agrees with the dossier submitter that **SHMG does not warrant classification for chronic hazards to the aquatic environment**.

RAC evaluation of hazards to the ozone layer

Summary of the Dossier Submitter's proposal

The dossier submitter proposed to not classify SHMG as hazardous to the to the ozone layer. The basis for this proposal is a low vapour pressure, a low Henry´s Law constant and rapid degradation through reaction with hydroxyl radicals for SHMG. Also SHMG is not listed in Annex I and II of Regulation (EC) No 1005/2009 of the European Parliament and of the Council of 16 September 2009 on substances that deplete the ozone layer.

Comments received during public consultation

Two MS commented and both agreed with the proposal to not classify SHMG as hazardous to the ozone layer.

Assessment and comparison with the classification criteria

RAC agrees with the dossier submitter to **not classify SHMG as hazardous to the ozone layer**.

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).

Annex 3 Minority opinion