Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SODIUM N-(HYDROXYMETHYL)GLYCINATE; [FORMALDEHYDE RELEASED FROM SODIUM N-(HYDROXYMETHYL)GLYCINATE]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: sodium N-(hydroxymethyl)glycinate; [formaldehyde released from sodium N-(hydroxymethyl)glycinate]
EC number: 274-357-8
CAS number: 70161-44-3
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Germany	European Federation for Cosmetic Ingredients AISBL	Industry or trade association	1

Comment received

· Sodium N-(hydroxymethyl)glycinate (SHMG, CAS No.: 70161-44-3) is an approved cosmetic preservative, with INCI name, Sodium Hydroxymethylglycinate.

It is listed in Annex V, LIST OF PRESERVATIVES ALLOWED IN COSMETIC PRODUCTS to Regulation (EC) No. 1223/2009 (the Cosmetics Regulation). Annex V stipulates a maximum concentration of 0.5% SHMG in cosmetic products and also the provision that products containing substances which release formaldehyde must include a warning label where the concentration of formaldehyde in the finished product exceeds 0.05%. This warning label is typically not necessary due to the low levels of formaldehyde in cosmetics.

As well as the stipulated maximum concentrations listed in Annex V, the Cosmetics Regulation specifies that cosmetic products must be safe for human health when used under normal or reasonably foreseeable conditions of use. A Safety Assessment carried out by a qualified safety assessor must demonstrate that cosmetic products are safe including exposure of products and their ingredients.

· SHMG is one of a group of formaldehyde releasing preservatives approved for use in cosmetic products. Each of these preservatives has its own reference with a maximum allowed concentration level in Annex V (EC) No. 1223/2009. A few of these are also used outside of the cosmetics industry and hence also fall within the scope of The Biocidal Products Regulation (BPR, Regulation (EU) 528/2012).

· It is widely recognised amongst regulators and stakeholders that there is a preservatives crisis within the cosmetics industry.

Preservatives typically are not effective against all microbial types, compatible with all cosmetic ingredients and suitable in all conditions, e.g. some pH ranges. Therefore, it is essential that a wide range of approved preservatives be available to afford full protection against a broad range of microorganisms. The commonly used cosmetic formaldehyde releasers are a vital tool in the palette of preservatives that formulators use in cosmetic products. The continued reduction in the number of approved preservatives available to the cosmetics industry has a number of consequences. These include the use of higher concentrations of remaining preservatives, less effective preservation systems and greater exposure to consumers of the same preservatives leading to potential development of safety issues.

· The Austrian Competent Authority's CLH Report on the proposal for harmonised classification and labelling of SHMG does not adequately address the use of SHMG in cosmetics, contains errors on the actual use levels and does not refer to the SHMG REACH Registration which contains the Registrant's classification and identified uses.

· EFfCI is concerned about the assumptions and conclusions, and without supporting evidence, made by the Austrian Competent Authority which are used to justify that classification of SHMG should be based on the theoretical concentration of releasable formaldehyde and that toxicity of formaldehyde should be used as read across for the toxicity of SHMG. These assumptions can be summarised from the following quotes in the CLH Report:

1.5 Short summary of the scientific justification for the CLH proposal
"Therefore we may theoretically assume a rate of 100% final hydrolysis in biological media."
"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."
"SHMG is proposed to be classified for carcinogenicity category 1B and mutagenicity category 2 based on the mechanistic considerations of total releasable amount of formaldehyde upon contact with biological media and read across of the carcinogenic and mutagenic property of formaldehyde."

In addition to the assumptions contained in the scientific justification, the proposal to classify SHMG, based on the theoretical concentration of releasable formaldehyde is not a hazard-based conclusion. The reliance on "releasable formaldehyde'' and similar terms related to SHMG toxicity in this proposal, is an implicit property of a risk assessment of possible exposure to formaldehyde. Therefore, the CLH report proposal is a hybridized conclusion of hazard classification and risk assessment processes. Consequently, the Austrian Competent Authority should reconsider its proposal by hazard classification only.

· The Austrian Competent Authority states in the CLH Report that "Due to the consideration that formaldehyde release is dominating the toxicity of SHMG and the classification of formaldehyde is read across to SHMG it is suggested that a specific note 8 is included for carcinogenicity (category 1B):" and that "Similarly for genotoxicity (category 2) a specific note 9 shall be included:". These proposed notes which would be assigned to the proposed SHMG entry in Annex VI to Regulation (EC) No. 1272/2008 and are as follows:
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%."
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%."

The inclusion of these notes against an SHMG harmonised entry will mean that a mixture

containing less than 0.1% theoretical concentration of releasable formaldehyde will not be classified as a Carcinogen or Mutagen. However, Regulation (EC) No. 1272/2008 does not apply to finished cosmetic products. Therefore, if that same mixture with less than 0.1% theoretical concentration of releasable formaldehyde is a cosmetic product then Article 15 of the Cosmetics Regulation could apply, prohibiting SHMG regardless of the theoretical formaldehyde level.
This resulting ban of an important cosmetic preservative is unprecedented and does not appear to be the intention of the Austrian Competent Authority in their report or in line with the wording of the Notes which indicates that there is no carcinogenicity concern for mixtures containing less than 0.1% theoretical concentration of releasable formaldehyde.
· This classification proposal is based on assumptions and read across and will have extreme consequences on the use of SHMG as used in cosmetics, the wider group of cosmetic formaldehyde releasing preservatives and ultimately the safety of cosmetic products. Therefore, EFfCI requests that more time is given to consideration of the alternative proposal. Specifically, that the relevant classification should be based on the actual measured values of free formaldehyde.

Dossier Submitter's Response

The concentrations for SHMG indicated in the CLP dossier (0.05% to 0.25%) relate to the use of SHMG as presented in the draft biocides CAR. Obviously this needs amendment for in use concentrations in the cosmetics sector. However in our understanding this would not significantly affect the scientific discussion.
With regard to the understanding of "intrinsic hazard" that should be the basis of classification, we would follow the view that the formaldehyde releaser has the intrinsic property to release formaldehyde and therefore consideration of maximal formaldehyde release is applicable for classification.
Note 8 and 9 would be part of the classification in Annex VI of Regulation (EC) No. 1272/2008. This note and consideration of safe use and the socioeconomic considerations provided here could be used for the application of Article 15 of the Cosmetics Regulation. However there is also the comment from Cosmetics Europe: "The inclusion of Formaldehyde Releasers (substance) used in finished cosmetic products currently does not trigger an article 15 procedure (CMR) under the Cosmetics Products Regulation since the level of free formaldehyde remains far below 0.1% in the substance". Anyway in our understanding this is out of the scope of the RAC discussion.
Measured values of free formaldehyde may not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reaction and constant shift of the equilibrium towards formaldehye release. Moreover we have already set a precedence with other formaldehyde releasers to consider total maximal formaldehyde release for classification. In our view new scientific data would be necessary to reopen this discussion.

RAC's response

RAC fully agrees with the DS's response

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Sweden		MemberState	2

Comment received

The dossier submitter has proposed to base classification of Sodium N-(Hydroxymethyl)glycinate on the data of the hydrolysis product formaldehyde. The Swedish CA supports classification of Sodium N-(Hydroxymethyl)glycinate as Muta. 2, H341 and Carc. 1B, H350.

Dossier Submitter's Response
Thank you for your review.
RAC's response
Your view is noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	3
Comment received				
The German CA agrees with the proposed classification.				
Dossier Submitter's Response				
Thank you for your review.				
RAC's response				
Your view is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium	Formaldehyde Biocide Interest Group (FABI)	Industry or trade association	4
Comment received				
The submission was made on behalf of the members of the Formaldehyde Biocides Interest Group (FABI), producers of formaldehyde releasers participating in the Biocidal Products Regulation (BPR) Review Programme. Sodium N-(hydroxymethyl)glycinate (SHMG, CAS 70161-44-3), belongs to a category of biocidal actives known as formaldehyde releasers. The FABI members provided input to the consultation considering that the classification proposal for SHMG is of relevance for all formaldehyde releasers. ECHA note – An attachment was submitted with the comment above. Refer to public attachment FABI_Public_Consultation_SHMG_Final.pdf				
Dossier Submitter's Response				
With regard to the understanding of "intrinsic hazard" that should be the basis of classification, we would follow the view that the formaldehyde releaser has the intrinsic property to release formaldehyde and therefore consideration of maximal formaldehyde release is applicable for classification. Moreover measured values of free formaldehyde may not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reaction and constant shift of the equilibrium towards formaldehye release. Moreover we have already set a precedence with other formaldehyde releasers to consider total maximal formaldehyde release for classification. In our view new scientific data would be necessary to reopen this discussion. All the key studies available in the REACH registration dossier for SHMG have been discussed in the CLH report and contributed to the CLH classification proposal for the hazard classes (HCs) with REACH registration data, i.e. acute tox (oral, inhalation, dermal), skin and eye irritation, skin sensitisation, repeated-dose toxicity and reprotoxicity. Although reference to the REACH registration data for those HCs is not explicitly indicated in the CLH report, we checked that the key studies presented in the REACH registration dossier were actually included in the CLH dossier. The socioeconomic considerations provided may support the use of SHMG in line with Article				

5(2) of the BPR.
RAC's response
RAC agrees with the understanding of the DS. Classification is based on the hazardous effects from the substance as such or its hydrolysis product, other cleavage products or any other metabolites is covered by the CLP Regulation. This is not a risk based approach.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium	Cosmetics Europe	Industry or trade association	5
Comment received				
There are several identified uses of SHMG in para 2.2 of CLH proposal. We want to highlight that SHMG is also present on Annex V of the Cosmetic Products Regulation 1223/2009 which is a list of authorized preservatives (entry number 51). The regulation permits the use of SHMG up 0.5% in all cosmetic products. Preservatives in general are important ingredients in cosmetic formulations to reduce the risk of microbial contamination of the product and to ensure the product remains suitable and safe during shelf-life and the period of use by consumers. Without preservatives, cosmetic products - just like food and other products handled directly by consumers - can become contaminated with microorganisms, leading to product spoilage, loss of product performance, and possibly irritation, infections or other adverse health reactions to the consumer. In the EU, cosmetics can only contain preservatives which are listed on Annex V to the Cosmetics Product Regulation (CPR) 1223/2009 (positive list concept). The CPR is mirrored by many Regulations worldwide; a well-functioning CPR is thus important for the cosmetics industry globally. For each formulation, a specific combination of different preservatives is needed to ensure microbial integrity throughout the products life cycle. Therefore, maintaining a wide and safe range of preservatives is of critical importance to the cosmetics sector. However, driven by safety, regulatory or perceived safety questions, the list of allowed preservatives for cosmetics in the EU is shrinking since several years and the development has now reached an alarming level, as has been agreed by the EU Commission and other stakeholders. Loss or further restrictions of this limited preservative palette will have serious implications for how to preserve cosmetics products in future: • The industry may be forced to use other Annex V preservatives which are less favourable for microbial efficacy and formulation compatibility. • Increased use of a limited number of preservatives by the industry could result in human health issues • Worst case, it could result in the loss of certain products categories and hinder innovation due to the inability to effectively preserve products whilst working within the Regulatory framework. Formaldehyde releasing preservatives are very efficient and unique preservatives and have a long history of safe use in cosmetic products. They are i) active over a large spectrum, of microorganisms (in particular towards potent Gram negative pathogens and specifically Pseudomonas aeruginosa and Burkholderia cepacia) and ii) versatile (high water solubility, active over a wide range of pH) so they may be used in various cosmetic product types. ECHA note – An attachment was submitted with the comment above. Refer to public attachment SHMG CE Public Consultation DRAFT Comments 26Oct2017 Final.zip				
Dossier Submitter's Response				
Chapter 2.2. obviously needs amendment for use in cosmetics. Note 8 and 9 would be part of the classification in Annex VI of Regulation (EC) No.				

1272/2008. This note and consideration of safe use and the socioeconomic considerations provided here could be applied to further support use for cosmetics. However in our understanding this is out of the scope of the RAC discussion. In our understanding measured values of free formaldehyde do not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reaction and constant shift of the equilibrium towards towards formaldehye release. Moreover we have already set a precedence with other formaldehyde releasers to consider total maximal formaldehyde release for classification. In our view new scientific data would be necessary to reopen this discussion.
RAC's response
The DS' view is fully supported.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Germany	European Federation for Cosmetic Ingredients AISBL	Industry or trade association	6

Comment received

1.5 Short summary of the scientific justification for the CLH proposal
"Therefore we may theoretically assume a rate of 100% final hydrolysis in biological media."
"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."
"SHMG is proposed to be classified for carcinogenicity category 1B and mutagenicity category 2 based on the mechanistic considerations of total releasable amount of formaldehyde upon contact with biological media and read across of the carcinogenic and mutagenic property of formaldehyde."

In addition to the assumptions contained in the scientific justification, the proposal to classify SHMG, based on the theoretical concentration of releasable formaldehyde is not a hazard-based conclusion. The reliance on "releasable formaldehyde'' and similar terms related to SHMG toxicity in this proposal, is an implicit property of a risk assessment of possible exposure to formaldehyde. Therefore, the CLH report proposal is a hybridized conclusion of hazard classification and risk assessment processes. Consequently, the Austrian Competent Authority should reconsider its proposal by hazard classification only.

· The Austrian Competent Authority states in the CLH Report that "Due to the consideration that formaldehyde release is dominating the toxicity of SHMG and the classification of formaldehyde is read across to SHMG it is suggested that a specific note 8 is included for carcinogenicity (category 1B):" and that "Similarly for genotoxicity (category 2) a specific note 9 shall be included:". These proposed notes which would be assigned to the proposed SHMG entry in Annex VI to Regulation (EC) No. 1272/2008 and are as follows:
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%."
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%."

The inclusion of these notes against an SHMG harmonised entry will mean that a mixture containing less than 0.1% theoretical concentration of releasable formaldehyde will not be classified as a Carcinogen or Mutagen. However, Regulation (EC) No. 1272/2008 does not

apply to finished cosmetic products. Therefore, if that same mixture with less than 0.1% theoretical concentration of releasable formaldehyde is a cosmetic product then Article 15 of the Cosmetics Regulation could apply, prohibiting SHMG regardless of the theoretical formaldehyde level. This resulting ban of an important cosmetic preservative is unprecedented and does not appear to be the intention of the Austrian Competent Authority in their report or in line with the wording of the Notes which indicates that there is no carcinogenicity concern for mixtures containing less than 0.1% theoretical concentration of releasable formaldehyde. · This classification proposal is based on assumptions and read across and will have extreme consequences on the use of SHMG as used in cosmetics, the wider group of cosmetic formaldehyde releasing preservatives and ultimately the safety of cosmetic products. Therefore, EFfCI requests that more time is given to consideration of the alternative proposal. Specifically, that the relevant classification should be based on the actual measured values of free formaldehyde.
Dossier Submitter's Response
With regard to the understanding of "intrinsic hazard" that should be the basis of classification, we would follow the view that the formaldehyde releaser has the intrinsic property to release formaldehyde and therefore consideration of maximal formaldehyde release is applicable for classification. Note 8 and 9 would be part of the classification in Annex VI of Regulation (EC) No. 1272/2008. This note and consideration of safe use and the socioeconomic considerations provided here could be used for the application of Article 15 of the Cosmetics Regulation. However there is also the comment from Cosmetics Europe: "The inclusion of Formaldehyde Releasers (substance) used in finished cosmetic products currently does not trigger an article 15 procedure (CMR) under the Cosmetics Products Regulation since the level of free formaldehyde remains far below 0.1% in the substance". Anyway in our understanding this is out of the scope of the RAC discussion. Measured values of free formaldehyde may not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reaction and constant shift of the equilibrium towards formaldehye release. Moreover we have already set a precedence with other formaldehyde releasers to consider total maximal formaldehyde release for classification. In our view new scientific data would be necessary to reopen this discussion.
RAC's response
Noted. RAC takes its decisions based on the criteria given in the CLP regulation and the data available. Which new data may – in future - be suitable to justify a re-opening of the discussion, needs critical analysis.

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Sweden		MemberState	7
Comment received				
The Swedish CA supports classification of Sodium N-(Hydroxymethyl)glycinate as Carc. 1B, H350.				
Dossier Submitter's Response				
Thank you for your review.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	United Kingdom	<confidential>	Company-Manufacturer	8

Comment received

pages 8 and 9

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf

Dossier Submitter's Response

IIa)
Measured values of free formaldehyde do not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reaction and constant shift of the equilibrium towards methylene glycol and further towards formaldehye release. In our understanding this ultimate formaldehyde release is also the presumed mode of action for biocidal activity. It would be unclear how SHMG would exert its biocidal activity, if not via continued formaldehyde release in response to contact with biological material. Moreover we have already set a precedence with other formaldehyde releasers to consider total maximal formaldehyde release for classification. In our view new scientific data would be necessary to reopen this discussion. With regard to potential of exposure, besides vapour pressour also aearosol formation needs to be considered.

IIb)
With regard to the understanding of "intrinsic hazard" that should be the basis of classification, we would follow the view that the formaldehyde releaser has the intrinsic property to release formaldehyde and therefore consideration of maximal formaldehyde release is applicable for classification.
We relied on the hydrolysis study submitted for the biocides evaluation, it is a GLP study and was considerd to fulfil Klimisch Score 2. We acknowledge that all studies are limited with regard to reproducibility and other uncertainties. However please note (as explained in our answer to point IIa) that the hydrolysis in water is not the core argument to support read across of the formaldehye hazard.
Please note that all the key studies available in the REACH registration dossier for SHMG have been discussed in the CLH report and contributed to the CLH classification proposal for the hazard classes (HCs) with REACH registration data, i.e. acute tox (oral, inhalation, dermal), skin and eye irritation, skin sensitisation, repeated-dose toxicity and reprotoxicity. Although reference to the REACH registration data for those HCs is not explicitly indicated in the CLH report, we checked that the key studies presented in the REACH registration dossier were actually included in the CLH dossier.

III)
Please note the first paragraph in the conclusions of the document you cited, CA-March15-Doc.5.1-final: "The principles of this note were endorsed at the 58th CA meeting and the annexes finalised at the 59th CA meeting after a final consultation between the Commission services, the evaluating competent authorities and the participants concerned."
Please also note that we have assessed SHMG as such. However since formaldehyde release is an intrinsic property of the formaldehyde releaser, also this property was considered for classification. See also our response to IIa).
Note 8 and 9 would be part of the classification in Annex VI of Regulation (EC) No. 1272/2008. This note and consideration of safe use and the socioeconomic considerations provided here could be applied to further support use for cosmetics. However there is also the comment from Cosmetics Europe: "The inclusion of Formaldehyde Releasers

(substance) used in finished cosmetic products currently does not trigger an article 15 procedure (CMR) under the Cosmetics Products Regulation since the level of free formaldehyde remains far below 0.1% in the substance". Anyway in our understanding this is out of the scope of the RAC discussion.

IVa)
We recommend to RAC to consider the classification proposal of Ashland for acute inhalation toxicity category 4. Our proposal relied on the data for the dry powder only, maybe this needs correction.

IVb)
We recommend to RAC to consider the arguments and conclusions of Ashland. We build our WoE proposal on the same data, but provide a different conclusion in the CLH report. Also experimental data contain uncertainties with regard to reproducibility and relevance. Therefore WoE approaches are always important and these should also include the conceptual consideration of the intrinsic property of a formaldehyde-releaser, i.e. releasing formaldehyde. Furthermore SHMG as manufactured (50% w/w solution) was not tested for skin irritation in the standard rabbit or standard in vitro tests.

IVc)
We recommend to RAC to consider the arguments and conclusions of Ashland. We build our WoE proposal on the same data. Also experimental data contain uncertainties with regard to reproducibility and relevance. For example the concordance estimate for repeated rabbit eye tests was reported as 65% for Cat 1/2/no cat classification (Barroso et al. 2017. Archives of Toxicology 91, 521-547, cited in OECD GD 263). Consequently WoE approaches are always important and these should also include the conceptual consideration of the intrinsic property of a formaldehyde-releaser, i.e. to release formaldehyde.

IVd)
We recommend to RAC to consider the arguments and conclusions of Ashland. We build our WoE proposal on the same data, but provide a different conclusion in the CLH report. In specific please note that positive scores in the study summarized in IIIA 6.1.5/02 were graded as 1 to 2 and this is used in line the the ECHA CLP Guidance for classification.

IVe)
We recommend to RAC to consider the arguments and conclusions of Ashland. We build our WoE proposal on the same data, but provide a different conclusion in the CLH report. In specific the negative systemic in vivo genotoxicity studies with SHMG are not considered sufficiently reliable. Also the systemic genotoxicity tests with formaldehyde are negative, the target sites were probably not reached, neither by SHMG, nor by formaldehyde.

IVf)
We recommend to RAC to consider the arguments and conclusions of Ashland. We build our WoE proposal on the same data, but provide a different conclusion in the CLH report.
Please note that local effects in the gastrointestinal tract were observed in the 28 day study. In principle such effects can develop into tumours upon long term exposure. A genotoxic mode of action contribution cannot be excluded. However for formaldehyde respiratory exposure was observed as the critical route for local tumour development. Respiratory studies with SHMG were neither available nor required.
Please note that our WoE conclusions differ from the conclusions from Ashland also for the other endpoints, and in our understanding the ultimate formaldehyde release is also the presumed mode of action for biocidal activity. It would be unclear how SHMG would exert its biocidal activity, if not via continued formaldehyde release in response to contact with

biological material.
In case the release of formaldehyde at the biological tissue site of contact is expected to be too slow to induce local carcinogenic effects, conceptually the concern for potential systemic carcinogenic effects would increase. Also experimental data contain uncertainties with regard to reproducibility and relevance. Therefore WoE approaches are always important and should also include the conceptual consideration of the intrinsic property of a formaldehyde-releaser, i.e. to release formaldehyde.
Please also note that physico-chemical and structural similarity of the source and target compounds is not necessarily required in the ECHA Read Across Assessment Framework (RAAF). The hypothesis applied corresponds conceptually to the ECHA 2015 RAAF scenario 1: "This scenario covers the analogue approach for which the read-across hypothesis is based on (bio)transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in a study conducted with one source substance are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) or absence of effect is predicted. The predicted strength of the effects may be similar or based on a worst case."
See also example 2 on pages 19/20 in the ECHA 2015 RAAF document.
Considering that toxicological testing is usually required up to doses or concentrations where adverse effects can be observed (maximum tolerated dose) and considering that the local irritative and genotoxic effects (at the site of contact) from formaldehyde release are the most critical effects to be expected - new carcinogenicity data for the reaction product were very unlikely to provide any new toxicological information and therefore due to animal welfare requirements unlawful to require.

V)
As repeatedly mentioned all experimental data contain uncertainties with regard to reproducibility and relevance. Therefore WoE approaches are important for classification and should also include the conceptual consideration of the intrinsic property of a formaldehyde-releaser, i.e. releasing formaldehyde.
From a regulatory point of view and in the absence of SHMG specific data for carcinogenicity and fertility, it is considered appropriate to build the classification based on available, submitted data and total WoE. Moreover the results of a SHMG specific carcinogenicity study are unlikely to provide any new toxicological information.

RAC's response

Where additional information was given by the commenter, this was considered in the opinion document. Otherwise RAC is in support of the DS' views.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium	Formaldehyde Biocide Interest Group (FABI)	Industry or trade association	9

Comment received

Please refer to the enclosed comments.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment FABI_Public_Consultation_SHMG_Final.pdf

Dossier Submitter's Response

See our response to comment No4, which includes also responses to the comments within the attachment from FABI.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium	Cosmetics Europe	Industry or trade association	10

Comment received

• There is a long history of safe use of SHMG in cosmetic products. SHMG use in cosmetics was considered safe by SCCS (SCCNFP/587/02). Glycine is an essential well-known amino acid and formaldehyde is released over the life time of the cosmetic product at very low levels, which ensures safe consumer use of cosmetic products preserved by SHMG.

• The present proposal to classify SHMG as Carc 1B seems to be solely based on the theoretical release of formaldehyde, classified as Carc 1B, not based on data relating to SHMG specifically.

• Cosmetic products preserved by Formaldehyde releasing preservatives only contain small amounts of free formaldehyde, i.e. usually less than 500ppm (0.05%), otherwise the finished cosmetic product would be labeled "contains formaldehyde" (EU Cosmetic Product Regulation). This labelling is not desired by Cosmetic manufacturers due to the consumer perception of formaldehyde.

• In a 2016 use survey of the EU cosmetic industry on preservative ingredient use, the mean concentrations of SHMG were significantly below 0.5% (maximum authorized level in Annex V of the European Cosmetic Regulation) and did not exceed 0.25% SHMG.

• As intended, formaldehyde is slowly released from preservatives of the Formaldehyde Releaser class over the life-time of the cosmetic product. Accordingly, free formaldehyde released at any given time point in the finished cosmetic product is far below the total theoretical level of free formaldehyde (far below 0.1%). The formaldehyde donor preservatives release small amounts of formaldehyde over time rather than all at once, which helps maintain product integrity during use. (Extract from page 474 of: J.F. Krowka, The importance of formaldehyde-donor preservatives in personal care products, Cosmetics & Toiletries magazine, Vol. 128, No. 7, July 2013)

• The inclusion of Formaldehyde Releasers (substance) used in finished cosmetic products currently does not trigger an article 15 procedure (CMR) under the Cosmetics Products Regulation since the level of free formaldehyde remains far below 0.1% in the substance.

• The assumed level of formaldehyde in SHMG is based on calculations of total theoretical formaldehyde and not on actual levels of free formaldehyde measured in SHMG to which the Cosmetics Industry does not agree.

• The method used to calculate the level of free formaldehyde is critical. Any measurement of free formaldehyde should relate to actual levels present in the substance.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment SHMG CE Public Consultation DRAFT Comments 26Oct2017 Final.zip

Dossier Submitter's Response

Note 8 and 9 would be part of the classification in Annex VI of Regulation (EC) No. 1272/2008. This note and consideration of safe use and the socioeconomic considerations provided here could be applied to further support use for cosmetics. However in our understanding this is out of the scope of the RAC discussion.

In our understanding measured values of free formaldehyde do not adequately mirror the exposure situation, where contact with biological tissues and fluids would lead to formaldehyde reaction and constant shift of the equilibrium towards towards formaldehye release. Moreover we have already set a precedence with other formaldehyde releasers to consider total maximal formaldehyde release for classification. In our view new scientific data would be necessary to reopen this discussion.
RAC's response
Noted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Sweden		MemberState	11
Comment received				
The Swedish CA supports classification of Sodium N-(Hydroxymethyl)glycinate as Muta. 2, H341.				
Dossier Submitter's Response				
Thank you for your review.				
RAC's response				
Noted and considered for the opinion document.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	United Kingdom	<confidential>	Company-Manufacturer	12
Comment received				
pages 7 and 8 ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf				
Dossier Submitter's Response				
Please see our response to comment 8 that includes responses to all endpoints commented by Ashland.				
RAC's response				
RAC does not follow Ashland's conclusions that 'the potential for mutagenic or genotoxic activity of SHMG is not conclusive to support classification.' The conclusion is based on the identical *in vitro/in vivo* data discussed in the CLH report. In Ashland's view, there are sufficient studies with the substance itself evidencing that there is no mutagenic effect (*in vivo*). By taking formaldehyde into account for a classification proposal for SHMG, the available negative *in vivo* studies are disregarded. This led to an incorrect conclusion. RAC points out that the CLP Guidance also regulates the *in vivo* testing as well as a possible classification of substances that can act only locally in soma cells at site of first contact due to their poor systemic availability. It can be 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 is taken into account that its hydrolysis product formaldehyde is already classified as Category 2 mutagen due to induction of local genotoxic effects.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	United Kingdom	<confidential>	Company-Manufacturer	13
Comment received				
page 6 ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf				
Dossier Submitter's Response				
Please see our response to comment 8 that includes responses to all endpoints commented by Ashland				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	14
Comment received				
Skin irritation (point 4.4.1.1, page 30): Please indicate the individual scores in the ISP study (1979) which trigger dermal irritation.				
Dossier Submitter's Response				
Please see document IIIA6.1.4/06 which is provided as an attachment to the CLH report and contains the study summary.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	United Kingdom	<confidential>	Company-Manufacturer	15
Comment received				
page 6 ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf				
Dossier Submitter's Response				
Please see our response to comment 8 that includes responses to all endpoints commented by Ashland				

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	16
Comment received				
Eye irritation (point 4.4.2.1, page 34 and point 4.4.2.5): According to Guidance on the Application of the CLP Criteria (version 5.0, page 310), it is stated that the current UNSCEGHS Guidance (adopted in June 2011) needs to be applied for older test methods. In the case of 6 rabbits, the following applies: "Classification for eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score per animal of ≥ 2 conjunctival erythema (redness). Therefore, the results in the eye irritation studies ISP (1990) and ISP (1979) are not considered "borderline to classification criteria for EU CLP category 2" since only 2 out 6 animals showed a redness score ≥ 2. It would be appreciated to indicate the GLP status for the first three studies mentioned in Table 4.4.2.1-1. Overall FR agrees with the conclusion.				
Dossier Submitter's Response				
Please see the attachments to the CLH report which contains the study summaries: *ISP (1990) Rabbit Eye Irritation in Study, PH421-SU-002-90; Doc IIIA 6.1.4/12:* ***GLP*** *ISP (1997) Primary Eye Irritation / Corrosion in Rabbits MB97-5686.04; Doc IIIA 6.1.4/08:* ***GLP*** *ISP (1979) Acute Eye Irritation in Rabbits, H-8712; Doc IIIA 6.1.4/09:* ***no GLP***				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	United Kingdom	<confidential>	Company-Manufacturer	17
Comment received				
page6 ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf				
Dossier Submitter's Response				
Please see our response to comment 8 that includes responses to all endpoints commented by Ashland				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	United Kingdom	<confidential>	Company-Manufacturer	18
Comment received				
page 7 ECHA note – An attachment was submitted with the comment above. Refer to public				

attachment Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf
Dossier Submitter's Response
Please see our response to comment 8 that includes responses to all endpoints commented by Ashland
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	19
Comment received				
Respiratory tract irritation (point 4.4.3, page 36): Although there is no specific data for respiratory tract irritation, it is stated that 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%). Please explain why this SLC was not considered whereas other SLCs are taken into account for acute toxicity studies, irritation and sensitization studies.				
Dossier Submitter's Response				
Thank you for your review and this observation. We recommend to RAC to consider also STOT SE 3, H335 classification.				
RAC's response				
Your point is taken and depends on whether classification as corrosive will be applied.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	20
Comment received				
FR agrees with the environmental assessment of the CLH report.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted by RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium		MemberState	21
Comment received				
Based on the data reported in the CLH report, BE CA agrees with the conclusion that classification of Sodium N-(hydroxymethyl)glycinate for the environment is not warranted : - Acute aquatic toxicity: LC50s for the substance as such and its degradation products are all >1 mg/L for all the 3 trophic level. - Chronic aquatic toxicity: the substance and his hydrolysis products are readily biodegradable and don't meet the criteria for bioaccumulation. Only a NOErC algae for the substance itself is available which is >1 mg/L. Tests with the hydrolysis product formaldehyde show NOECs for 3 trophic levels>1 mg/l. QSAR estimates for the hydrolysis product Sodiumglycinate/glycine points towards no chronic aquatic toxicity.				

Several references are made to the biocidal dossier. Please don't refer to the tables and chapters but include all relevant information in the CLH report in order to have a complete and clear view on the available data.
Dossier Submitter's Response
Thank you for comment. Unfortunaley it is not possible to update the CLH Report at this stage. However since it will not change the conclusion on this endpoint we consider that the relevant information is compiled in the CLH Report.
RAC's response
Noted by RAC.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	22
Comment received				
In accordance with the information provided in the CLH report, the reason for no classification "data lacking" for the hazard classes "Gases under pressure", "Pyrophoric liquids" and "Pyrophoric solids" should be changed to "conclusive but not sufficient for classification" in table 1.3-1.				
Dossier Submitter's Response				
Agreed, the reason for no classification should be changed to "conclusive but not sufficient for classification".				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. Ashland Response To The CLH Report For Sodium N-(Hydroxymethyl)glycinate.pdf [Please refer to comment No. 8, 12, 13, 15, 17, 18]
2. FABI_Public_Consultation_SHMG_Final.pdf [Please refer to comment No. 4, 9]
3. SHMG CE Public Consultation DRAFT Comments 26Oct2017 Final.zip [Please refer to comment No. 5, 10]