Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

9-[2-(Ethoxycarbonyl)phenyl]-3,6-bis(ethylamino) -2,7-dimethylxanthenium chloride; Basic Red 1

EC Number: 213-584-9
CAS Number: 989-38-8

CLH-O-0000007031-88-01/F

Adopted

16 September 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 9-[2-(ETHOXYCARBONYL)PHENYL]-3,6-BIS(ETHYLAMINO)-2,7-DIMETHYLXANTHYLIUM CHLORIDE; BASIC RED 1

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride; Basic Red 1
EC number: 213-584-9
CAS number: 989-38-8
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2020	Sweden		MemberState	1
Comment received				
In table 2 of the CLH proposal, the Dossier Submitter states that the current CLH in CLP Annex VI Table 3.1 is Skin Sens. 1B, H317. This seems to be a typing error since the substance currently lacks harmonised classification for skin sensitisation (as also stated in Table 6 and section 3 of the CLH proposal). In the section on evaluation of health hazards, the Dossier Submitter has provided information on the registrants read-across argumentation and refers to data provided from the registrant from the QSAR toolbox showing that the target and source substances are very similar. However, no further detail is provided in the CLH proposal on which similarities the Dossier Submitter refer to. It would be helpful if the Dossier Submitter could elaborate on which parameters indicate similarities between the target and source substances (e.g. structural analogues, skin sensitisation predictions).				
Dossier Submitter's Response				
The German CA appreciates the comments. There is currently no harmonised classification for skin sensitisation, therefore in table 2 is a typing error. The registrants read-across hypothesis including the results from the QSAR toolbox is included as confidential annex.				
RAC's response				
Thank you for your comments. Noted				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
10.11.2020	Finland		MemberState	2
Comment received				
In the only available acute oral toxicity study (similar to OECD TG 401), the LD50 value of 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride was 250 mg/kg bw in rats based on mortality. An ATE of 250 mg/kg bw is therefore warranted. According to the CLP Regulation, a substance shall be classified as Acute Tox. 3, H302 if the ATE value is > 50 and ≤ 300 mg/kg bw. FI CA supports the proposed classification of Acute Tox. 3; H302 for 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride.				
Dossier Submitter's Response				
The German CA appreciates the support.				
RAC's response				
Thank you for your comments. Agreed, however the MSCA erroneously refers in its comment to H302 (harmful if swallowed) instead of H301 (toxic if swallowed).				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
10.11.2020	Finland		MemberState	3
Comment received				
Only one pre-guideline study (similar to OECD TG 405, deviations described below) is available for the evaluation of the serious eye damage/eye irritation potential of 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride in rabbits. Iris score and conjunctivae score were not measured in the study, but chemosis and cornea opacity showed scores of 3-4 (with corrosion and ulceration) for both test animals at 24 hours. These lesions were irreversible after the observation period of eight days. The FI CA agrees that this timeframe is sufficient for the establishment of the magnitude and irreversibility of the lesions, also from the animal welfare point of view. The proposed classification of Eye Dam. 1; H318 for 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride is supported.				
Dossier Submitter's Response				
The German CA appreciates the support.				
RAC's response				
Thank you for your comments. Agreed				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
10.11.2020	Finland		MemberState	4
Comment received				
The skin sensitisation potential of the read-across substance 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)phenyl]-2,7-dimethylxanthylium chloride has been investigated in one reliable local lymph node assay (LLNA) in mice. In the study, stimulation indices of 3.0 (± 0.8), 5.7 (± 1.6) and 3.6 (± 1.2) were determined at concentrations of 10, 25 and 50%				

of the test substance, respectively. An EC3 value of 10% was calculated. According to the CLP Regulation, a substance may be classified as a skin sensitiser if the stimulation index is ≥3 in the LLNA. This criterion is fulfilled at all test concentrations. In addition, the result allows subcategorisation as the EC3 value is >2%, hence meeting the criterion for sub-category 1B.

9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride is considered to react in the same way as the read-across substance 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)phenyl]-2,7-dimethylxanthylium chloride based on the information provided by the DS. There is no information available on skin sensitisation in humans. FI CA supports the proposed classification of Skin Sens. 1B; H317 for 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride.

Dossier Submitter's Response

The German CA appreciates the support.

RAC's response

Thank you for your comments.
Noted, however since lower concentrations than 2% were not tested, classification in category 1A could not formally be excluded. Taking into account the lack of linear dose response relationship (SI values of 3.0 ± 0.8, 5.7 ± 1.6 and 3.6 ± 1.2 at concentrations of 10, 25 and 50%, correlation coefficient r=0.07, very weak or no correlation), extrapolation of results to lower concentrations is not appropriate. ECHA CLP Guidance indicates that, when Category 1A cannot be excluded, Category 1 (as a default) should be applied instead of Category 1B, particularly when results at lower doses are absent or in the absence of adequate dose-response information. Therefore, classification as Skin Sens 1, H317 (May cause an allergic skin reaction), without sub-categorisation is proposed by RAC for Basic Red 1.

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2020	Sweden		MemberState	5

Comment received

In the CLH-proposal the Dossier Submitter presents results from a positive LLNA test in mice. It is stated that the reliability of the study is 2: reliable with restriction. The SE CA notes that reliability 1 (reliable without restriction) is stated on ECHA's dissemination site. It is not evident from the CLH proposal what the Dossier Submitter considers to be the limitations of the study and what the implications are for the interpretation of the results (and consequently for the classification).

The LLNA study is performed with 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)-phenyl]-2,7-dimethylxanthylium chloride (Basic Red 1:1) and read-across is made from this substance for the assessment and classification of 9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride (Basic Red 1) . Consequently, the same conclusion and resulting classification is applicable to the source substance as the target substance. It would be appreciated if the Dossier Submitter could elaborate on the reason why harmonised classification is not proposed for 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)-phenyl]-2,7-dimethylxanthylium chloride (Basic Red 1:1) as well.

The SE CA agrees that the substance has skin sensitising potential since SI ≥ 3 were observed at the tested concentrations (10%, 25 and 50% (v/v)). An EC3 > 2 indicates that a classification in category 1B is warranted. However, classification in category 1A

could not formally be excluded since lower concentrations than 10% were not tested. The SE CA also notes that there is a lack of linear dose response relationship (SI values of 3.0 ± 0.8, 5.7 ± 1.6 and 3.6 ± 1.2 at concentrations of 10, 25 and 50% (v/v)). Extrapolation of results to lower concentrations is therefore not appropriate. The dose response relationship has not been analysed or discussed in the CLH proposal.

The SE CA further notes that the source substance 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)-phenyl]-2,7-dimethylxanthylium chloride (Basic Red 1:1) is expected to have low to moderate solubility (log Pow = 1.7 at 20 °C (pH 7)) in the selected vehicle acetone/olive oil (4:1 v/v) in the available LLNA. It would be interesting if the Dossier Submitter could elaborate on the possible implication the choice of vehicle could have on the solubility of the test substance and the outcome of the study.

Overall, the SE CA concurs with the Dossier Submitter that the substance is a skin sensitiser in Category 1, based on the results of the LLNA study. Sub-categorisation is however not possible based on the available data.

Dossier Submitter's Response

The German CA appreciates the comments and agrees that harmonised classification should also be considered for the source substance (Basic Red 1:1).
The available data on skin sensitisation lacks information on choice of vehicle and dose selection. Therefore, based on the dose selection, lack of information on a dose-response at lower doses and on solubility of the substance in the vehicle chosen, category 1A (although unlikely) cannot formally be excluded. A discussion in RAC is welcomed, if Category 1B or no subcategorisation (and therefore Category 1) is more suitable in this case.

RAC's response

Thank you for your comments.
RAC agrees that Category 1A cannot be excluded, thus Category 1 (as a default) should be applied instead of Category 1B, particularly when results at lower doses are absent or in the absence of adequate dose-response information. Therefore, classification as Skin Sens 1, H317 (May cause an allergic skin reaction), without sub-categorisation is proposed by RAC for Basic Red 1.
Note to vehicle choice: based on study report for LLNA study with Basic red 1:1 [ECHA website: https://echa.europa.eu/pl/registration-dossier/-/registered-dossier/25449/7/5/1] "Details on study design: PRE-SCREEN TESTS - Compound solubility: The vehicle was selected on the basis of maximising the solubility".