Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

1-phenylethan-1-one (1-phenylethylidene)hydrazone

EC Number: 211-979-0
CAS Number: 729-43-1

CLH-O-0000007030-90-01/F

Adopted

16 September 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1-PHENYLETHAN-1-ONE (1-PHENYLETHYLIDENE)HYDRAZONE

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.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: 1-phenylethan-1-one (1-phenylethylidene)hydrazone
EC number: 211-979-0
CAS number: 729-43-1
Dossier submitter: France

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.10.2020	Germany		MemberState	1
Comment received				
We support the classification of 1-phenylethan-1-one (1-phenylethylidene)hydrazone (CAS no. 729-43-1) as skin sensitiser. Four human cases (children and adult) are reported, showing that the substance elicited positive patch test reactions. The well-conducted studies show a relationship between sports equipment (shin pads, sneakers)-induced contact dermatitis and the role of 1-phenylethan-1-one (1-phenylethylidene)hydrazone in skin sensitisation. Classifi-cation is supported by positive results from in vitro studies for skin sensitisation and alerts for skin sensitisation based on QSAR modelling. In contrast, in an LLNA (Klimish score 1) ace-topnenone azine did not show a sensitisation potential at concentrations of 1 %, 2.5 % and 5 % (SI values: 0.7, 0.4, and 0.5), challenging a strong skin sensitising potential of 1-phenylethan-1-one (1-phenylethylidene)hydrazone. However, 1-phenylethan-1-one (1-phenylethylidene)hydrazone was identified as a new emerging substance to cause skin aller-gies in humans (more case reports have been published recently) with to some extent high severities of responses (hospitalisation and generalised dermatitis). Based on the available data, we support the classification of 1-phenylethan-1-one (1-phenylethylidene)hydrazone as Skin Sens.1, without sub-categorisation. A recommendation for the GCL or SCL should be given.				
Dossier Submitter's Response				
Thank you for your supportive comments. SCLs for skin sensitisation are generally set based on the results from animal testing based on potency. However the LLNA study is negative. Based on human data available, acetophenone azine gave strong reactions with positive patch test results until 0.001%. However further data are needed to sub-categorize or set a limit concentration for acetophenone azine. To be discussed with RAC members.				

RAC's response
Your support for classification of acetophenone azine as skin sensitizer is noted. RAC agrees with DS that the data is too limited to propose a SCL. The LLNA study does not allow to conclude on potency, and the reported human cases do not provide sufficient information on exposure.

Date	Country	Organisation	Type of Organisation	Comment number
22.10.2020	Belgium		Individual	2
Comment received				
Bonjour, Mon fils (10 ans) développe un eczéma allergique très sévère au contact avec une substance chimique particulière (acétophénone azine) qui est en consultation actuellement sur le site de l'ECHA. Propositions CLH: 5 • Date de début: 24/08/2020 • Date limite: 23/10/2020 Il est suivi par le service dermatologie des cliniques universitaires St Luc à BRUXELLES (Docteurs <confidential> et <confidential>) Cette substance est présente dans les équipements sportifs. Il est important qu'elle puisse être identifiée par un étiquetage spécial afin que les consommateurs puissent l'éviter en cas d'allergie. D'avance, je vous remercie. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment photos GL.docx				
Dossier Submitter's Response				
Thank you for your supportive comments. We noted that this information confirm the results of previous relevant published clinical cases in child and adult and that acetopheone azine is a skin sensitizer.				
RAC's response				
Comment and additional information is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.10.2020	Sweden		MemberState	3
Comment received				
In the CLH-proposal the dossier submitter presents 4 case reports of 3 children and one adult with allergic skin reactions to 1-phenylethan-1-one (1-phenylethylidene)hydrazone from shin pads and shoes. Some of the cases report severe reactions (one case with hospitalization and one with generalized dermatitis) indicating that 1-phenylethan-1-one (1-phenylethylidene)hydrazone is a potent skin sensitizer. Following the submission of the CLH-dossier at least 2 more case reports have been published (see references below). The human data is supported by two positive in vitro test results from key events 2 (OECD TG 442D; Keratinosens) and 3 (h-CLAT; OECD TG 442E) in the AOP for skin sensitisation. These two in vitro tests are included in the "2 out of 3" defined approach that is not yet accepted by the OECD for assessing skin sensitisation potential, but since the results of the two tests are concordant the SE CA considers that the outcome can be used to indicate such potential. Moreover, the available data is further supported by alerts for skin sensitisation potential by QSAR modeling (Derek Nexus and Caesar). QSAR				

modeling is a widely accepted in silico tool for prediction of health hazards of substances.

The dossier submitter also presents results from a negative LLNA test in mice, including a discussion on findings that could point to that it may be a false negative. The SE CA agrees that a SI>3 could not be excluded since the maximum concentration tested was low (only 5%) and that the results from the positive and negative controls are somewhat conflicting. On the other hand, from the lack of clear dose response (SI values of 0.7, 0.4 and 0.5 at concentrations of 5, 2.5 and 1% (w/v)) there is little indication that using a higher concentration would result in a much higher SI value. It would be helpful if the dossier submitter could elaborate on the rationale behind the dose selection in the study.

The evidence of the skin sensitizing properties of 1-phenylethan-1-one (1-phenylethylidene) hydrazone presented by the dossier submitter is in our view limited. However, there are positive findings from at least 4 human patch tests that cannot be negated by the LLNA test results. Moreover, it cannot be excluded that the low number of current cases could reflect that the substance has not yet been used for a sufficient period for more cases to emerge, and/or underreporting. The in vitro/silico data presented in the CLH-report supports the skin sensitizing properties demonstrated by the human patch tests and additional new studies in the scientific literature could be used as further evidence. Overall, the SE CA concurs with the dossier submitter that the substance is a skin sensitizer in Category 1 based on a weight of evidence assessment and using expert judgement. Sub-categorization is not possible based on the reported results.

1) Koumaki D, Bergendorff O, Bruze M, Orton D. Allergic Contact Dermatitis to Shin Pads in a Hockey Player: Acetophenone Is an Emerging Allergen. Dermatitis. 2019 Mar/Apr;30(2):162-163.
2) Besner Morin C, Stanciu M, Miedzybrodzki B, Sasseville D. Allergic contact dermatitis from acetophenone azine in a Canadian child. Contact Dermatitis. 2020 Jul;83(1):41-42.

Dossier Submitter's Response

Thank you for your supportive comments.

Concerning the selection of doses tested in LLNA study, (annex I):
A preliminary irritation/toxicity was performed according to a study plan on CBA/CaOIaHsd mice using four doses (1 animal/dose) with the concentrations of 5, 0.5, 0.05 and 0,005% (w/v) in DMF. Based on the results of this study, 5% (w/v) dose was selected as top dose for the main test. Then the other tested doses of 2.5 and 1% were chosen according guideline 429 in the main test.

Thank you for bringing to our attention the new case reports. CLH report can no longer be modified at this stage, but we note these case reports you refered to confirm our conclusions concerning the classification proposal.
For the follow up of the process, they are briefly summarized below:
The first United Kingdom case with severe allergic contact dermatitis caused by the presence of acetophenone azine in shin pads of a 17 year old hockey player was reported by Koumaki *et al*. in 2019. Patch test gave positive reactions to acetophenone at 1%, 0.01% and 0.001% in acetone.
Besner Morin *et al.* in 2020 reported a new case of acetophenone azine-induced shin pad and sports shoe dermatitis in a North American 6 year-old soccer player. The child

reacted positively to acetophenone azine in a suitable vehicle petrolatum at 1% and 0.1% acetophenone azine. These new clinical findings confirm the results of previous relevant published clinical cases in child and adult : acetophenone azine is suspected as a skin sensitizer. The published cases are summarised in a table attached to the comments.
RAC's response
Thank you for the additional case studies. They are now included in the opinion. With respect to the dose and vehicle selection for the LLNA test, RAC observes that these were established in a preliminary study in accordance with OECD TG 429. Concetrations of up to 100% were tested in several solvents, however in terms of capabilities for physical formulation (i.e., solubility) only the 5% solution in DMF was found to be acceptable for the main study. The results from the preliminary and main studies are documented in the Annex to the CLH report.

CONFIDENTIAL ATTACHMENTS
1. photos GL.docx [Please refer to comment No. 2]