Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,4-dimethylcyclohex-3-ene-1-carbaldehyde [1];
(1α,2α,5α)-2,5-dimethylcyclohex-3-ene-1-carbaldehyde [2]; 2,6-dimethylcyclohex-3-ene-1-carbaldehyde [3];
3,5-dimethylcyclohex-3-ene-1-carbaldehyde [4];
3,6-dimethylcyclohex-3-ene-1-carbaldehyde [5];
4,6-dimethylcyclohex-3-ene-1-carbaldehyde [6];
Reaction mass of 3,5-dimethylcyclohex-3-ene-1-carbaldehyde and 2,4-dimethylcyclohex-3-ene-1-carbaldehyde [7]; dimethylcyclohex-3-ene-1-carbaldehyde [8]; Dimethylcyclohex-3-ene-1-carbaldehyde [9];
1,2,4(or 1,3,5)-trimethylcyclohex-3-ene-1-carbaldehyde [10];
1,3,4-trimethylcyclohex-3-ene-1-carbaldehyde [11];
2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde [12];
2,4,6-trimethylcyclohex-3-enecarbaldehyde [13];
isocyclocitral [14]; 3,5,6-trimethylcyclohex-3-ene-1-carbaldehyde [15]; 4,6,6-trimethylcyclohex-3-ene-1-carbaldehyde [16];

EC Number:
268-264-1 [1]; 252-395-6 [2]; - [3]; 268-263-6 [4]; 267-186-5 [5]; 253-139-6 [6]; - [7]; 248-742-6 [8]; 272-113-5 [9]; 276-055-1 [10]; - [11]; - [12]; 215-833-7 [13]; 215-638-7 [14]; 266-810-3 [15]; - [16]

CAS Number:
68039-49-6 [1]; 35145-02-9 [2]; 6975-94-6 [3]; 68039-48-5 [4]; 67801-65-4 [5]; 36635-35-5 [6]; - [7]; 27939-60-2 [8]; 68737-61-1 [9]; 71832-78-5 [10]; 40702-26-9 [11]; 1726-47-2 [12]; 1423-46-7 [13]; 1335-66-6 [14]; 67634-07-5 [15]; 6754-27-4 [16];

CLH-O-0000007204-81-01/F

Adopted
1 December 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CYCLOHEX-3-ENE-1-CARBALDEHYDE DERIVATIVES

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: Cyclohex-3-ene-1-carbaldehyde derivatives:
2,4-dimethylcyclohex-3-ene-1-carbaldehyde [1];
(1α,2α,5α)-2,5-dimethylcyclohex-3-ene-1-carbaldehyde [2];
2,6-dimethylcyclohex-3-ene-1-carbaldehyde [3];
3,5-dimethylcyclohex-3-ene-1-carbaldehyde [4];
3,6-dimethylcyclohex-3-ene-1-carbaldehyde [5];
4,6-dimethylcyclohex-3-ene-1-carbaldehyde [6];
Reaction mass of 3,5-dimethylcyclohex-3-ene-1-carbaldehyde and 2,4-dimethylcyclohex-3-ene-1-carbaldehyde [7];
dimethylcyclohex-3-ene-1-carbaldehyde [8];
dimethylcyclohex-3-ene-1-carbaldehyde [9];
1,2,4(or 1,3,5)-trimethylcyclohex-3-ene-1-carbaldehyde [10];
1,3,4-trimethylcyclohex-3-ene-1-carbaldehyde [11];
2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde [12];
2,4,6-trimethylcyclohex-3-enecarbaldehyde [13];
isocyclocitral [14];
3,5,6-trimethylcyclohex-3-ene-1-carbaldehyde [15];
4,6,6-trimethylcyclohex-3-ene-1-carbaldehyde [16]

EC number: 68-264-1 [1]; 252-395-6 [2]; - [3]; 268-263-6 [4]; 267-186-5 [5]; 253-139-6 [6]; - [7]; 248-742-6 [8]; 272-113-5 [9]; 276-055-1 [10]; - [11]; - [12]; 215-833-7 [13]; 215-638-7 [14]; 266-810-3 [15]; - [16]

CAS number: 68039-49-6 [1]; 35145-02-9 [2]; 6975-94-6 [3]; 68039-48-5 [4]; 67801-65-4 [5]; 36635-35-5 [6]; - [7]; 27939-60-2 [8]; 68737-61-1 [9]; 71832-78-5 [10]; 40702-26-9 [11]; 1726-47-2 [12]; 1423-46-7 [13]; 1335-66-6 [14];6 7634-07-5 [15]; 6754-27-4 [16]

Dossier submitter: Germany

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2022	France		MemberState	1
Comment received				
Experimental data with substance members 1, 7, 8, 14 lead to a consistent conclusion as Skin Sens. 1 or Skin Sens. 1B. As some of these substances also show skin irritating				

potential, could you please confirm if the concentrations used in the sensitisation assays are correctly chosen according to existing guidelines?
The GPMT with substance member 2 is negative but the concentrations seems too low to adequately identify sensitisation effects (5% for topical induction and 1% for challenge application).
Altogether these data suggest a low potency of sensitisation.

Human data is available with substance members 5, 7, 8, 9 and 14, with positive results only obtained with substance member 9. It should be noted that study with substance member 9 was performed with selected patients whereas the tests with the other members were performed on healthy volunteers. Moreover, some of these negative studies were carried out with lower concentrations than the concentration used in the positive study. Consistently with experimental data, human data suggest a low potency of sensitisation.

Inconsistent findings were obtained in vitro with substance member 13.

All members have at least one skin sensitisation alert from in silico estimations.

Based on structural and physico-chemical similarities and results from studies above, France agrees with the proposed classification as Skin Sens. 1B for the substances considered in the CLH report. This is consistent with most of the notified classifications available with these substances.

Dossier Submitter's Response

Concerning the skin irritating potential and the concentrations used in the sensitisation assays:
OECD TG 406 (GPMT and Buehler test) states that "*the concentration of test chemical used for each induction exposure should be well-tolerated systemically and should be the highest to cause mild-to-moderate skin irritation. The concentration used for the challenge exposure should be the highest non-irritant dose*".

In the GPMT (OECD TG 406) performed with the test substance EC no. 268-264-1 (Anonymous, 2018), used concentrations based on a range-finding test. "*The concentration for intradermal induction (1% and 5% w/v in arachis oil BP) was selected by using 2 guinea pigs receiving different concentrations. The highest concentration that caused only mild to moderate skin irritation was selected for the intradermal induction stage of the main study.* […] *In addition, the concentration for topical challenge (50%, 25%, 10%, and 5% v/v in ethanol/diethylphthalate 1:1) was also selected following the highest non-irritant concentration of the test material and one lower concentration was selected for the topical challenge stage of the main study*" (ECHA dissemination site, last accessed 01.06.2022).

According to OECD TG 429 (LLNA), "*all existing toxicological information (e.g. acute toxicity and dermal irritation) and structural and physicochemical information on the test substance of interest (and/or structurally related test substances) should be considered where available, in selecting the three consecutive concentrations so that the highest concentration maximises exposure while avoiding systemic toxicity and/or excessive local skin irritation*".

In the LLNA performed with EC no. 248-742-6 (Calvert, 2012), a study report was not available. However, the registrant cited that "*in general, the doses were selected so that the highest concentration maximizes exposure while avoiding systemic toxicity and*

excessive local irritation. Doses were selected based on known reported uses of the material." Furthermore, clinical observation revealed that "*No erythema or oedema was noted in any of the mice in the vehicle group or in those dosed with the test article*" and that "*There were no other findings*" (ECHA dissemination site, last accessed 01.06.2022). In the LLNA (OECD TG 429) with the substance EC no. 215-638-7 (Syngenta CTL, 2006; submitted in the registration dossier of EC no. 215-833-7) "*Dose levels were set by the sponsor in accordance with the acute oral toxicity data provided*". No clinical observations were reported, including signs of skin irritation in tested animals. For other animal studies conducted with the substances EC nos. 267-186-5, 215-638-7, or substance No. 7 (no identifier) of the dossier detailed study information was not available (Reliability 4) and therefore information on a range-finding test or the selection of the concentration were missing. The Dossier Submitter thanks for the comment and appreciates the support of the FR CA.
RAC's response
Thank you for your comment. RAC agrees with the Dossier Submitter's response.