Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

α-methyl-1,3-benzodioxole-5-propionaldehyde [1]

**(*S*)-α-methyl-1,3-benzodioxole-5-propionaldehyde;
(2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal [2]**

**(*R*)-α-methyl-1,3-benzodioxole-5-propionaldehyde;
(2*R*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal [3]**

EC Number: 214-881-6 [1];- [2]; - [3]
CAS Number: 1205-17-0 [1]; 737776-68-0 [2]; 737776-59-9 [3]

CLH-O-0000007094-76-01/F

Adopted

18 March 2022

18 March 2022

CLH-O-0000007094-76-01/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: **α-methyl-1,3-benzodioxole-5-propionaldehyde [1]**

(*S*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal [2]

(*R*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2R)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal [3]

EC Number: **214-881-6 [1], - [2], - [3]**

CAS Number: **1205-17-0 [1], 737776-68-0 [2], 737776-59-9 [3]**

The proposal was submitted by **Denmark** and received by RAC on **1 June 2021.**

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

PROCESS FOR ADOPTION OF THE OPINION

Denmark 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 **9 August2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **8 October 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anca Oana Docea**

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 **18 March 2022** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	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	605-RST-VW-Y	α-methyl-1,3-benzodioxole-5-propionaldehyde; [1] (*S*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal; [2] (*R*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*R*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal; [3]	214-881-6 [1] - [2] - [3]	1205-17-0 [1] 737776-68-0 [2] 737776-59-9 [3]	Skin Sens. 1B	H317	GHS07 Wng	H317			
RAC opinion	605-RST-VW-Y	α-methyl-1,3-benzodioxole-5-propionaldehyde; [1] (*S*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal; [2] (*R*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*R*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal; [3]	214-881-6 [1] - [2] - [3]	1205-17-0 [1] 737776-68-0 [2] 737776-59-9 [3]	Skin Sens. 1B	H317	GHS07 Wng	H317			
Resulting Annex VI entry if agreed by COM	605-RST-VW-Y	α-methyl-1,3-benzodioxole-5-propionaldehyde; [1] (*S*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal; [2] (*R*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*R*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal; [3]	214-881-6 [1] - [2] - [3]	1205-17-0 [1] 737776-68-0 [2] 737776-59-9 [3]	Skin Sens. 1B	H317	GHS07 Wng	H317			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

α-Methyl-1,3-benzodioxole-5-propionaldehyde, also known as helional, CAS no. 1205-17-0 is a multi-constituent substance, consisting of two isomeric forms: (2*R*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal, CAS no. 737776-59-9 and (2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal CAS 737776-68-0. None of these chemicals has an existing CLP regulation entry. Registered uses of helional for consumers include washing and cleaning products, air care products, polishes and waxes, perfumes and fragrances, cosmetics and personal care products and biocides (e.g. disinfectants, pest control products). Registered uses for professionals include washing and cleaning products, polishes and waxes and biocidal products (e.g. disinfectants, pest control products). The proposal from the dossier submitter (DS) recommend the classification of helional as Skin Sens. 1B, H317. The need for classification is justified by the DS by the existing differences in self-classification of the chemical and the discrepancy seen in the C&L notifications for helional. Helional is registered in a high tonnage (100-1000 t/yr), and has widespread consumer and uses professional uses in applications that may entail dermal exposure.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS reported the following animal study on the skin sensitising properties of helional (cf. Table 10.1 of the CLH report and Table 1 and 2 of its annex I):

Method, guideline, deviations if any	OECD Guideline 429 - Skin Sensitisation: Local Lymph Node Assay (LLNA) Deviations: No justification for the concentration series or use of EtOH:DEP as a vehicle was available
Species, strain, sex, no/group	Mouse, CBA/Ca, females Five dose groups, n=4 Control-groups: One vehicle control, three positive control groups (PC), and one vehicle control for the positive control group.
Test substance	α-methyl-1,3-benzodioxole-5-propionaldehyde (helional) 95 $\geqslant$ Conc. (% (w/w)) $\leqslant$ 99 Vehicle: 1:3 Ethanol/Diethylphthalate (EtOH:DEP) PC: Substance: Hexyl cinnamic aldehyde (CAS no. 101-86-0)
Dose levels **Duration of exposure**	Dose-groups 0, 2.5, 5, 10, 25 and 50 % (w/v) in 1:3 (EtOH:DEP) PC group 5, 10 and 25 % (w/v) preparation in acetone:olive oil (4:1) Vehicle control group: 1:3 EtOH:DEP

	Exposure: 25 µL of the preparation was applied to the dorsal surface of the ear on day 1-3.
Results	**Vehicle Control group (VC)** – Stimulation index (SI) – N/A **Dose groups** 2.5%(w/v) – SI 1 – Negative (SI<3) 5%(w/v) – SI 2.7 – Negative (SI<3) 10%(w/v) – SI 2.4 – Negative (SI<3) 25%(w/v) – SI 3.8 – Positive (SI>3)[1] 50%(w/v) – SI 8.3 - Positive (SI>3) **EC3: 16.4 %** **Positive control (PC) group** Vehicle (PC) – SI – N/A HCA 5%(w/v) – SI 1.5 – Negative (SI<3) HCA 10%(w/v) – SI 2.2 – Negative (SI<3) HCA 25%(w/v) – SI 6.6 –Positive (SI ⩾ 3)
Reference	Unnamed study report, 2005
Klimisch score	1

[1] Animal no. 59 in group 4 died during thymidine dosing and was hence excluded from the study.

The DS also reported a clinical study that supports the animal study results (cf. Table 10.2 of the CLH report and Table 3 of its Annex I):

Type of data/report	Clinical case study, according to European Society of Contact Dermatitis (ESCD) 'Guideline for diagnostic patch testing – recommendations on best practice'.
Patients included	494 consecutive dermatitis patients, aged ≥18 years, were divided into 5 group as follows: 100 patients in 3.0 % w/w group 104 patients in 4.5 % w/w group 103 patients in 6.8 % w/w group 100 patients in 10.1 % w/w group 87 patients in 15.2 % w/w group
Test substance	Helional CAS no. 1205-17-0 Purity ≥ 98%
Relevant information about the study (as applicable)	The purpose of the study was to find the optimal patch test concentration for testing three widely used sensitising fragrance substances including helional.
Dose levels **Duration of exposure**	Dose groups: 3.0 %, 4.5 %, 6.8 %, 10.1 % and 15.2 % w/w helional. The patch tests were conducted by applying 20 mg of

	helional suspended in petrolatum to the upper back in Finn Chambers (8mm; SmartPractice, Phoenix, Arizona). Occlusion time two days. Reading was performed on day 2-5 and day 7. Interim evaluations of the patch test results were performed to assess the individual concentrations before increasing (by 50 %) or decreasing (by 33 %) in the next dose group as described in the ESCD Guideline
Results	3.0 % w/w – Positive reactions 0/100; Doubtfull reactions 0/100; Irritant reaction 0/100 4.5 % w/w - Positive reactions 2/104; Doubtfull reactions 0/104; Irritant reaction 0/104 6.8 % w/w - Positive reactions 1/103; Doubtfull reactions 0/103; Irritant reaction 0/103 10.1 % w/w - Positive reactions 0/100; Doubtfull reactions 0/100; Irritant reaction 1/100 15.2 % w/w - Positive reactions 1/87; Doubtfull reactions 1/87; Irritant reaction 0/87 Four (0.8 %, 95 % CI [0.3-2.1 %]) of 494 consecutive dermatitis patients had positive patch test reactions to the different tested concentrations of helional. The authors concluded that a clear allergic reaction is shown to helional and a patch test concentration for screening purposes of 7.5 % petrolatum (3.0 mg/cm2) was identified.
Reference	Bennike et al., 2019

Two studies are available on the sensitising properties of helional: one LLNA that confirmed its skin sensitizing properties, and a study on human patch tests that supported the animal study results. In the adopted opinion of the Scientific Committee on Consumer Safety (SCCS 2011), helional is categorized as an established contact allergen in animals with an estimated concentration needed to produce a SI of 3 (EC3) value of 16.4%. The three Defined Approaches included in the OECD support document also categorized helional as a skin sensitizer.

The *in vivo* study from 2005 is an OECD TG 429 LLNA study in mice conducted under GLP conditions. The tested concentration levels were 2.5, 5, 10, 25 and 50 % (w/v) in 1:3 Ethanol/Diethylphtalate (EtOH:DEP). The positive control chemical hexylcinnamaldehyde gave a $\geqslant$ 3-fold proliferative response at 25 % (w/v) concentration. In the case of helional, the $\geqslant$ 3-fold proliferative response was obtained at concentrations 25 and 50 % (w/v) with SI values of 3.8 and 8.3, respectively. The calculated EC3 was 16.4 % (w/v). The study met the CLP criteria for helional as a skin sensitiser.

The deviation from OECD TG 429 is determined by the use of EtOH:DEP that is not a standard recommended solvent. EtOH:DEP is frequently used to assess dermal effects of fragrance material in humans and animal studies. The study by Betts et al. (2007), that evaluated the use of EtOH:DEP solvent as an alternative of acetone:olive oil (AOO) in LLNA assay, concluded AOO is suitable for the test as EtOH:DEP induces a background proliferative lymph node response similar to that of AOO. For example, in the citral (CAS no. 5392-40-5) CLH proposal, the use of

EtOH:DEP was accepted as a solvent in the LLNA test and subsequently considered the studies for harmonized classification and labelling.

The Bennike et al. 2019 human patch test study supports the classification of helional as a skin sensitizer. The study aimed to identify an optimal patch test concentration for three widely used sensitising fragrances, including helional (purity $\geqslant$ 98 %). It was a well-conducted study using a protocol published by the European Society of Contact Dermatitis (ESCD) and following the ESCD 'Guideline for diagnostic patch testing – recommendations on best practice'. 494 dermatitis patients, aged $\geqslant$ 18 years, were referred to the department of Dermatology and Allergy, Copenhagen University Hospital Herlev and Gentofte (Hellerup, Denmark) and tested in five different dose groups (n $\approx$ 100). The tested concentrations were 3.0, 4.5, 6.8, 10.1 and 15.2 % (w/w) with an occlusion time of two days. The reading of the test results was performed on day 2-5 and day 7. Interim evaluations of the patch test results were performed to assess the individual concentration and if it should be increased (by 50 %) or decreased (by 33 %) in the next group of approximately 100 patients. From the 494 patch tests only four (0.8 %, 95 % confidence interval 0.3-2.1 %) had a positive result to helional. No induced contact allergy was suspected or identified, assuming that no false-positive responses were included. Based on the obtained results the recommendations of the study were that the patch testing concentration is 7.5 % helional in petrolatum (w/w).

The design of the study was to identify an optimal patch test concentration and not a diagnostic patch test study identifying a reliable frequency of already sensitised individuals suitable to be used for classification. There were three dose groups lower than the identified optimal patch test concentration of 7.5 % helional. False-negative results cannot therefore be overruled. It is possible that a patch test study conducted with 7.5 % helional could result in a frequency higher than 0.8 %.

Comments received during consultation

Two comments were received from Member State Competent Authorities. Both supported the classification of helional as Skin Sens. 1B. One MSCA asked if there are specific data with patch tests performed with 10.1 % and 15.2 % helion to support the statement that the frequency of occurrence of skin sensitisation can be > 0.8 % since patch tests included concentrations < 7.5 % helional (considered as optimal concentration).

The DS responded that the study by Bennike et al. (2019) identifying the optimal patch test concentration for helional included approximately 100 patients per test concentration. One positive reaction was seen at 15.2 %. The data are also summarised in Annex I. Based on the results optained in the study, the DS is of the opinion that it cannot be excluded that a higher frequency of sensitisation would be seen in a clinical patch test study, using the identified optimal patch test concentration of helional.

Another comment from a MSCA was related to the statement that helional was subjected to *in vitro* testings leading to classification as Skin Sens. 1 or 1B depending on the defined approach considered. This supports the proposed classification. Thus, it would have been interesting to add more information in the CLH report on these *in vitro* tests and their results, if possible.

DS responded that has not looked further into the *in vitro* data behind the classification derived from the guideline on Defined Approaches for Skin Sensitisation (DASS). Since the data used on reference chemicals in the supporting document and its annexes have been thoroughly evaluated in the process of developing the DASS, the DS is of the opinion that the classification derived from the DASS can be used as supporting evidence.

One MSCA asked if relative exposure data, data on the induction threshold of helional in humans, or data on the severity of responses in patients were available or were considered (in a weight of evidence approach for sub-categorisation) to conclude that "human data can therefore not exclude helional to have strong sensitising properties in humans".

The DS answered that they had not been able to indentify data on the induction threshold of helional in humans. The only human data identified was the study by Bennike et al. (2019) identifying the optimal patch test concentration of helional. All four positive reactions were scored as ++ positive reactions (+/++/+++). Data on the human exposure to helional were lacking, therefore relative exposure data were not considered in the CLH dossier. In the 2012 SCCS opinion helional is mentioned as a "top 100 substance" referring to volumes used. The registred tonnage is 100-1000 t/yr with widespread uses by both consumers and professional workers in applications that may entail dermal exposure. However, no data on observed concentrations in consumer products have been available to the DS enabling an exposure consideration according to guidance on application of CLP criteria.

Assessment and comparison with the classification criteria

The CLP regulation Annex I, section 3.4.2.2. Skin sensitisers allow the classification of skin sensitisers in one hazard category, Category 1, which comprises two sub-categories, 1A and 1B.

Data and criteria for the classification of helional as a skin sensitiser:

According to Table 3.4.2, section 3.4.2.2.1.4. of the CLP regulation (1272/2008), for category 1 the substances shall be classified in accordance with the following criteria: *" if there are positive results from an appropriate animal test (see specific criteria in*

paragraph 3.4.2.2.4.1)", or "*if there is evidence that the substance can lead to sensitisation by skin contact in a substantial number of persons…*".

In vivo animal study provided by REACH registration dossier (Unnamed study report, 2005) is a LLNA study conducted according to OECD 429 under GLP conditions, reliable without restrictions that can be used for classification. The helional showed a SI $\geqslant$ 3, and thereby a positive response as a skin sensitiser Category 1.

The study of Bennike et al. (2019) showed positive reactions in 0.8% unselected consecutive dermatitis patients in patch test with helional. There are concerns that 0.8% could be underestimated based on the arguments previously discussed. Thus the human data also justify the classification of helional as a skin sensitiser, Category 1.

Sub-category of helional:

The CLP regulation, section 3.4.2.2.1.2 provides the criteria to classify a substance as skin sensitiser as 1A: strong sensitisers and 1 B: other skin sensitisers when data are available and sufficient for classification. Sections 3.4.2.2.3.2 and 3.4.2.2.3.3 from CLP regulation described data from animal studies that can be used to categorise a substance in one of the two sub-categories. For the LLNA an EC3 value $\leqslant$ 2% determine the classification of the substance as 1A, while an EC3 value > 2% determines the classification of the substance as 1B. In the case of helional, the LLNA study identified an EC3 value of 16.4% that was above 2%, so the criteria in table 3.4.4, section 3.4.2.2.3.3 is fulfilled and sub-category 1B is applicable.

As supporting evidence for this classification, the data from the OECD "Supporting document for evaluation and review of draft Guideline (GL) for Defined Approches (DAs) for Skin Sensitisation" (2019) lists helional as a substance for which (high quality) LLNA data predicts the GHS potency

sub-category of 1B, refering to the same study. Also the Bennike et al. (2019) confirmed helional to be a human skin sensitiser and identified the optimal patch test concentration to be 7.5 %. For this reason, a diagnostic patch test study with the recommended concentration of 7.5 % helional could potentially result in a higher frequency of sensitisation. Thus the frequency of 0.8 % identified in Bennike et al. (2019) may underestimate the incidence of sensitisation in an unselected population. The human data can therefore not exclude helional to have strong sensitising properties in humans.

Overall conclusion: The available animal data identifies helional as a skin sensitiser with a low to moderate potency relevant for sub-category 1B. Human data support the classification of helional as a skin sensitiser, Category 1, and does not exclude the possibility of it being a stronger sensitiser in humans. There is no scientific information identified for setting a specific concentration limit (SCL) so the generic concentration limit for the sub-category 1B (1% w/v) will apply.

Therefore, RAC agrees with the DS to **classify α-methyl-1,3 benzodioxole-5-propionaldehyde and its enantiomers as Skin Sens. 1B; H317.**

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).