Committee for Risk Assessment

RAC

Annex 1

Background document

to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

18 March 2022

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

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

EC Number: **214-881-6 [1]**

CAS Number: **1205-17-0 [1]**

737776-68-0 [2]

737776-59-9 [3]

Index Number:

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Version number: 2 **Date: 01.06.2021**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON α-METHYL-1,3-BENZODIOXOLE-5-PROPIONALDEHYDE

CONTENTS

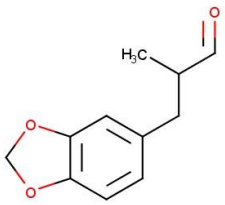
ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON α-METHYL-1,3-BENZODIOXOLE-5-PROPIONALDEHYDE

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1.1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	(1,3-benzodioxol-5-yl)-2-methyl propanal; 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal; 2-Methyl-3-(3,4-methylenedioxyphenyl)propionaldehyde; 3-(1,3-Benzodioxol-5-yl)-2-methylpropanal; 3-(2H-1,3-benzodioxol-5-yl)-2-methylpropanal; 3-(3,4-methylenedioxyphenyl)-2-methylpropanal; 5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione; alpha-Methyl-1,3-benzodioxole-5-propionaldehyde; alpha-Methyl-3,4-methylene-dioxyhydrocinnamicaldehyde [1] (*S*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*S*)-3-(2H-1,3-benzodioxol-5-yl)-2-methylpropanal; (2*S*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal [2] (*R*)-α-methyl-1,3-benzodioxole-5-propionaldehyde; (2*R*)-3-(2H-1,3-benzodioxol-5-yl)-2-methylpropanal; (2*R*)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal [3]
Other names (usual name, trade name, abbreviation)	Helional Heliofresh Heliofesh Heliogan Heliproponal HLF MMDHCA
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	214-881-6 [1]
EC name (if available and appropriate)	α-methyl-1,3-benzodioxole-5-propionaldehyde
CAS number (if available)	1205-17-0 [1]; 737776-68-0 [2]; 737776-59-9 [3]
Other identity code (if available)	-
Molecular formula	$C_{11}H_{12}O_3$

Structural formula	
SMILES notation (if available)	CC(CC1=CC2=C(C=C1)OCO2)C=O [1] O=C[C@@H](C)Cc1ccc2OCOc2c1 [2] O=C[C@H](C)Cc1ccc2OCOc2c1 [3]
Molecular weight or molecular weight range	192.21 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	The substance is a multi-constituent substance, consisting of two isomeric forms. The entry also includes the separate stereoisomers.
Description of the manufacturing process and identity of the source (for UVCB substances only)	Helional is not an UVCB.
Degree of purity (%) (if relevant for the entry in Annex VI)	Addressed in the confidential annex.

1.2 Composition of the substance

Table 1.2: Constituents (non-confidential information)

Constituent	Concentration range (% w/w)	Current CLH in Annex VI Table 3 (CLP)	Current self- classification and labelling (CLP)
(2R)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal CAS no. 737776-59-9	Addressed in confidential annex.	None	Skin Sens. 1B; H317 Repr. 2; H361 Aquatic Chronic 2; H411
(2S)-3-(1,3-benzodioxol-5-yl)-2-methylpropanal CAS no. 737776-68-0	Addressed in confidential annex.	None	Skin Sens. 1B; H317 Repr. 2; H361 Aquatic Chronic 2; H411

Information of impurities in the substance are confidential and are addressed in the confidential annex attached to this report.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 2.1: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	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 submitter's proposal	TBD	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]	1205-17-0 [1] 737776-68-0 [2] 737776-59-9 [3]	Skin Sens. 1B	H317	GHS07 Wng	H317			

Table 2.2: Reason for not proposing harmonised classification and status under public consultation

Hazard class	**Reason for no classification**	**Within the scope of public consultation**
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation		
Skin sensitisation	**Harmonised classification proposed**	**Yes**
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

3 PREVIOUS CLASSIFICATION AND LABELLING

The substance helional (CAS no. 1205-17-0) has no current harmonised classification in Annex VI of the CLP regulation. In all 1662 C&L notifications have been submitted to ECHA, of which approximately 30% have classified helional "Skin Sens. 1" and approximately 7% have classified helional "Skin Sens. 1B". C&L notifications have been submitted for the individual stereoisomers (CAS no. 737776-68-0 and CAS no. 737776-59-9), with one notifyer classifying “Skin Sens. 1B” for each isomer.

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.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Differences in self-classification
Disagreement by DS with majority of current self-classifications

Further detail on need of action at Community level

The substance falls under article 36 (3) and 37 (1) of the CLP Regulation. The justification for the proposal is Dossier Submitters concern about the discrepancy seen in the C&L notifications. Currently (September 2020) there are 1662 notifications in the C&L inventory and only 615 notifiers (37 %) classify helional as a skin sensitiser (category 1 or 1B). The REACH registrants classify helional as a skin sensitiser category 1B. The remaining 1047 notifiers (63%) do not classify for skin sensitisation. Helional is registrered in a high tonnage (100-1000 t/yr), and the widespread uses of helional include both consumer uses and uses by professional workers in applications that may entail dermal exposure. The Dossier Submitter is concerned that users of the substance do not receive sufficient information through labelling and/or through Safety Data Sheets (SDS) to take relevant precautions.

In an adopted opinion of the Scientific Committee on Consumer Safety (SCCS, 2011), helional is categorized as an established contact allergen in animals. Helional is listed as a fragrance substance used in high volumes (the document refers to the substance as a 'top 100' substance), and a substance of which human data are lacking (SCCS, 2011).

OECD (2019) mentions helional in the '*Supporting document for evaluation and review of draft Guideline (GL) for Defined Approaches (DAs) for Skin Sensitisation'*. Three DAs are included in this support document for a draft guideline, i.e. "The 2 out of 3", "The integrated testing strategy version 1" (ITSv1) and "The integrated testing strategy version 2" (ITSv2). These three DAs have been shown to either provide the same level of information or be more informative than the rodent Local Lymph Node Assay (LLNA; OECD TG 429) for identification of skin sensitising substances. Further ITSv1 and ITSv2 can provide information on sub-categorization according to the CLP criteria. The DAs all categorize helional as a skin sensitiser, and the two DAs which can provide sub-categorization, categorize the substance in the sub-category of 1B (OECD, 2019).

The International Fragrance Association (IFRA) has limited the concentration of helional in consumer products, with standard limits ranging from 0.026 % to 12 % and last implementation date in 2022 (IFRA 2020). With the new limits in finished products, IFRA has lowered the general maximum limits from previous publications on helional (IFRA, 2013).

A harmonised classification of helional as a skin sensitiser in sub-category 1B will lead to labelling requirements for substances and for mixtures containing the substance. The classification of helional will lead to a generic concentration limit of ≥ 1 % and will further lead to the special labelling requirements for mixtures containing > 0.1 % to protect already sensitised individuals.

The Dossier Submitter has scrutinised all available data on helional relevant to the end-point of skin sensitisation, including data from a literature search conducted in February 2020. On that basis, the Dossier Submitter has prepared the present proposal for a harmonised classification of helional as a skin sensitiser, Category 1B.

5 IDENTIFIED USES

Data in the publicly available part of the REACH registration dossier for helional (March 2020) identify the following uses:

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).

6 DATA SOURCES

The primary source of information was the REACH registration dossier for helional (CAS no. 1205-17-0) (February 2020). The key study (Unnamed study report, 2005) was available to Dossier Submitter in the form of a Chemical Safety Report (CSR) and the original study report. The information in the proposal is cited from the publicly available part of the REACH registration dossier.

Information was further supplied by data found in a literature search.

A literature search was conducted in February 2020.

The literature search included both scientific and other open literature. It was conducted using all identified chemical names related to the CAS no. 1205-17-0 and numerical identifiers.

Databases used: ECHA, Wiley, Elsevier, Web of Science, Google Scholar, Google, PubMed, OpenGrey and the Royal Danish Library (REX). In addition, articles were obtained by a review of the reference lists of relevant articles.

Relevance of retrieved articles were first examined by title, then by abstract and lastly (where relevant) by review of the whole text.

7 PHYSICOCHEMICAL PROPERTIES

Table 7.1: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid	REACH registration dossier	-
Melting/freezing point	< -20 °C	REACH registration dossier	-
Boiling point	294.85 – 295 °C	REACH registration dossier	@101.5 – 102.1 kPa
Relative density	1.16	REACH registration dossier	@ 20 ± 0.5 °C
Vapour pressure	0.0923 Pa	REACH registration dossier	@22 -24 °C
Surface tension	-	REACH registration dossier	Study waived
Water solubility	934 mg/L	REACH registration dossier	@20±0.5 °C
Partition coefficient n-octanol/water	Log Kow = 2.4	REACH registration dossier	@25 °C
Flash point	144 ± 2 °C	REACH registration dossier	-
Flammability	-	REACH registration dossier	Study waived
Explosive properties	-	REACH registration dossier	Study waived
Self-ignition temperature	364 ± 5 °C	REACH registration dossier	@100.9 – 101.1 kPa
Oxidising properties	-	REACH registration dossier	Study waived
Granulometry	-	REACH registration dossier	Study waived
Stability in organic solvents and identity of relevant degradation products	-	REACH registration dossier	Study waived
Dissociation constant	-	REACH registration dossier	Data not provided by registrant
Viscosity	-	REACH registration dossier	Data not provided by registrant

8 EVALUATION OF PHYSICAL HAZARDS

Hazard classes not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Hazard class not assessed in this dossier.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Hazard class not assessed in this dossier

10.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier

10.3 Acute toxicity - inhalation route

Hazard class not assessed in this dossier

10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier

10.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier

10.6 Respiratory sensitisation

Hazard class not assessed in this dossier

10.7 Skin sensitisation

Two studies were identified, one animal study and one human study, given in table 10.1 and 10.2, respectively. The animal study (LLNA) is included in the REACH registration dossier. Helional has not been evaluated to be acute toxic according to the CLP criteria or to have irritating effects.

Table 10.1: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	OECD 429 – LLNA Deviations: No justification for selection of the concentration series or use of EtOH:DEP as a vehicle was available in the summary or in the study report.
Species, strain, sex, no/group	Mouse, CBA/Ca, females Five dose groups, n=4 Control-groups: One vehicle control, three positive control groups, and one vehicle control for the positive control group. Hexylcinnamaldehyde was used as positive control with acetone:olive oil 4:1 (AOO) as vehicle.
Test substance	A-methyl-1,3-benzodioxole-5-propionaldehyde (helional) CAS no. 1205-17-0 EC no. 214-881-6
Dose levels Duration of exposure	Dose-groups 0, 2.5, 5, 10, 25 and 50 % (w/v) in 1:3 Ethanol/Diethylphthalate (EtOH:DEP) Exposure: 25 µL of the preparation was applied to the dorsal surface of the ear on day 1-3.
Results	The test substance caused skin sensitisation when applied in 25 and 50 % w/v preparations, with Stimulation Index (SI) of 3.8 and 8.3, respectively. EC3: 16.4 % Overall assessment: sensitising substance.
Reference	Unnamed study report, 2005
Klimisch score	1

Table 10.2: Summary table of human data on skin sensitisation

Type of data/report	Clinical case study
Test substance	Helional CAS no. 1205-17-0
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. The following concentrations of helional were used in the study: 3.0 %, 4.5 %, 6.8 %, 10.1 % and 15.2 %.
Observations	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 % pet. (3.0 mg/cm^2) was identified.
Reference	Bennike et al., 2019

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Two studies on the sensitising properties of helional have been identified. The LLNA study confirms helional to be a skin sensitiser. One publication on sensitising properties of helional seen in human patch tests is available, also confirming helional to be a skin sensitiser. SCCS (2011) mentions helional as a fragrance substance categorised as established contact allergen in animals referring to the Estimated Concentration needed to produce a SI of 3 (EC3) value of 16.4 %. In addition, as mentioned in chapter 4, the three DAs included in the OECD support document, all categorize helional as a skin sensitiser.

10.7.1.1 Animal data

One relevant *in vivo* study has been identified: Unnamed study report, 2005.

The OECD 429 LLNA study in mice was conducted under GLP conditions. The concentration levels of the test substance were 2.5, 5, 10, 25 and 50 % (w/v) in 1:3 Ethanol/Diethylphtalate (EtOH:DEP). Hexylcinnamaldehyde was used as a positive control and resulted in a ≥ 3-fold proliferative response at 25 % (w/v) concentration. The test substance, helional, gave a ≥ 3-fold response at concentrations 25 and 50 % (w/v), with SI values of 3.8 and 8.3 respectively. The EC3 was calculated to be 16.4 % (w/v) (4100 µg/cm^2).

Under the conditions of the study helional was considered by the authors to be a skin sensitiser.

EtOH:DEP, which is not one of the standard recommended vehicles in the OECD 429 test guideline, was used as vehicle in the study. However, EtOH:DEP is frequently used to assess dermal effects of fragrance materials in both human and experimental studies. In a comparative study, EtOH:DEP was investigated as an alternative vehicle to acetone:olive oil (AOO). The study concluded that EtOH:DEP is a suitable vehicle for use in the LLNA (Betts, et al., 2007). The use of EtOH:DEP as a vehicle in the LLNA has been discussed in previous CLH proposals, e.g. citral (CAS no. 5392-40-5). In the RAC Opinion proposing harmonised classification and labelling of citral, the use of EtOH:DEP was discussed and the data was accepted relevant to use for classification purposes (ECHA, 2018).

10.7.1.2 Human data

One relevant publication with human patch test data has been identified: Bennike et al., 2019.

The objective of the study was to identify an optimal patch test concentration for three widely used sensitising fragrances including helional (CAS no. 1205-17-0, purity ≥ 98 %). The study was conducted using a protocol published by the European Society of Contact Dermatitis (ESCD). An optimal test concentration is to be used for diagnostic patch testing (identification of the responsible contact allergen(s) in patients who suffer from contact dermatitis or to exclude contact allergy). An optimal test concentration elicits an allergic response in those previously sensitised and cause no positive reaction in those who are not allergic (Johansen et al., 2015).

484 consecutive dermatitis patients, aged ≥ 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 ≈ 100). 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. No patients experienced contact allergy (skin sensitisation) induced by the test and no more than a few irritant reactions were registered, which lead to an increase in all steps. ESCD '*Guideline for diagnostic patch testing – recommendations on best practice*', was followed regarding exclusion criteria and scoring of patch test results.

A starting concentration of 3.0 % (w/w) was used for patch testing helional followed by concentrations of 4.5 %, 6.8 %, 10.1 % and 15.2 %, with an occlusion time of two days. Reading was performed on day 2-5 and day 7.

Of the 494 patch tests performed, four (0.8 %, 95 % confidence interval: 0.3-2.1 %) had a positive result to helional. Bennike et al. (2019) did not identify or suspect any induced contact allergy (skin sensitisation) and thus it is assumed that the study data includes no false positive responses.

The study resulted in recommendations of patch testing concentration of 7.5 % helional in pet. (w/w) (3.0 mg/cm2). The author of the study reports of clearly allergic positive patch test reactions to helional.

The study was designed to identify an optimal patch test concentration and did not conduct a diagnostic patch test[1] study, which would identify a reliable frequency of already sensitised individuals suitable to be used for classification. Thus, three dose-groups included in the study were lower than the identified optimal patch test concentration of 7.5 % helional. The study may therefore include false negatives, as the concentration used in the lower dose groups might have been too low to elicit an allergic reaction. It is therefore possible that a patch test study conducted with 7.5 % helional could result in a frequency higher than 0.8 %.

10.7.2 Comparison with the CLP criteria

In the following, the identified data for helional as a skin sensitiser are compared to the classification criteria of the CLP regulation (1272/2008) Annex I, section 3.4.2.2. *skin sensitisers*. The CLP regulation allows 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

"...For Category 1, a stimulation index of three or more is considered a positive response in the local lymph node assay."

CLP regulation (1272/2008) Annex I, section 3.4.2.2.3.1.

The study provided in the REACH registration dossier (Unnamed study report, 2005) describes a LLNA according to OECD Guideline 429 and is evaluated to be reliable without restrictions, and can be used directly for classification. The LLNA study with helional showed a SI ≥ 3, and thereby a positive response as a skin sensitiser Category 1.

In addition, Table 3.4.2 (CLP, section 3.4.2.2.1.4.) states:

"*.. Substances shall be classified as skin sensitisers (Category 1)… if there is evidence that the substance can lead to sensitisation by skin contact in a substantial number of persons…*"

Bennike et al. (2019) provided data which showed positive reactions in 0.8 % unselected consecutive dermatitis patients. However, the 0.8 % might be an underestimation as discussed above. Dossier Submitter evaluates the study to provide data showing that helional has led to sensitisation by skin contact in a substantial number of individuals, and thus support the classification of helional as a skin sensitiser, Category 1.

Sub-category of helional

When data are available and sufficient a skin sensitiser can be allocated to one of the two sub-categories, 1A: strong sensitisers and 1B: other skin sensitisers (CLP regulation, section 3.4.2.2.1.2).

The CLP regulation (1272/2008), section 3.4.2.2.3.2 and 3.4.2.2.3.3 describes data from animal studies which can be used to categorise a substance in one of the two sub-categories.

The LLNA study identified an EC3 value for helional of 16.4 %. As the EC3 value was above 2 %, sub-category 1A is not applicable according to the criteria in CLP regulation, table 3.4.3, section 3.4.2.2.3.2., and may be exluded.

[1] "*Diagnostic patch testing is an investigation undertaken on patients with a history of dermatitis (eczema) in order to determine whether they have a contact allergy and then evaluate the relation (if any) of the contact allergy to their dermatitis.*." Johansen, et al., 2015.

As the EC3 value of 16.4 % was above 2%, the criteria in table 3.4.4, section 3.4.2.2.3.3 is fulfilled and sub-category 1B is applicable.

OECD (2019) has helional listed as a substance of which (high quality) LLNA data predicts GHS potency sub-category of 1B, referring to the above described study.

As discussed above, 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.

10.7.3 Conclusion on classification and labelling for skin sensitisation

The reviewed animal data identifies helional as a skin sensitiser with a low to moderate potency – sub-category 1B. Human data supported the data showing helional as a skin sensitiser, Category 1, however the data could not exclude helional to be a stronger sensitiser in humans. Overall the Dossier Submitter proposes a classification of Skin sens. 1B; H317: May cause an allergic skin reaction.

No scientific information has been identified to set a specific concentration limit (SCL) and the generic concentration limits of the sub-category 1B (1 % w/v) should be used.

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	*a*-methyl-1,3-benzodioxole-5-propionaldehyde (helional) 95 ⩾ Conc. (% (w/w)) ⩽ 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 the skin sensitiser properties of helional, and a study on human patch tests that also 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 ⩾ 3-fold proliferative response at 25 % (w/v) concentration. In the case of helional, the ⩾ 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 solvent 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 ⩾ 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 ⩾ 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 ≈ 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 the MSCAs. 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.**

10.8 Germ cell mutagenicity

Hazard class not assessed in this dossier

10.9 Carcinogenicity

Hazard class not assessed in this dossier

10.10 Reproductive toxicity

Hazard class not assessed in this dossier

10.11 Specific target organ toxicity-single exposure

Hazard class not assessed in this dossier

10.12 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this dossier

10.13 Aspiration hazard

Hazard class not assessed in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Hazard class not assessed in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Hazard class not assessed in this dossier

13 ADDITIONAL LABELLING

Skin sensitisers, sub-category 1B, has the generic concentration limit triggering classification of a mixture of ≥ 1.0 %. To protect individuals who are already sensitised to the substance, a lower concentration limit for elicitation is used. According to CLP Table 3.4.6., mixtures containing ≥ 0.1 % of a skin sensitiser in category 1B should be subject to the specific labelling requirements of section 2.8 of Annex II.

A mixture containing ≥ 0.1 % helional should therefore use the statement:

EUH208 – 'Contains helional. May produce an allergic reaction'

REFERENCES

Bennike, N.H., Zachariae, C., Johansen, J.D. (2019). Optimal patch testconcentration for three widely used sensitizing fragrance substances without mandatory labelling in cosmetics. Contact Dermatitis, 2019, 80, 325-327.

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Unnamed study report, 2005 (cited from the publicly available REACH registration dossier available online at ECHA website).

14 ANNEXES

ANNEX I

Confidential ANNEX

Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

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]

Index Number:

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Tolderlundsvej 5, 5000 Odense, Denmark

Version number: 1 **Date: 02.10.2020**

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON α-METHYL-1,3-BENZODIOXOLE-5-PROPIONALDEHYDE

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON α-METHYL-1,3-BENZODIOXOLE-5-PROPIONALDEHYDE

CONTENTS

1 PHYSICAL HAZARDS

Hazard classes not assessed in this dossier

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Hazard classes not assessed in this dossier

3 HEALTH HAZARDS

3.1 Acute toxicity

Hazard class not assessed in this dossier

3.2 Skin corrosion/irritation

Hazard class not assessed in this dossier

3.3 Serious eye damage/eye irritation

Hazard class not assessed in this dossier

3.4 Respiratory sensitisation

Hazard class not assessed in this dossier

3.5 Skin sensitisation

3.5.1 Animal data

3.5.1.1 Anonymous, 2005

Study reference

Anonymous, 2005. Information retrived from the publicly available REACH registration dossier.

Detailed study summary and results

An OECD 429 Local Lymph Node Assay (LLNA) study in mice was conducted under GLP conditions. The concentration levels of the test substance, helional (CAS no. 1205-17-0), were 2.5, 5, 10, 25 and 50 % (w/v) in 1:3 Ethanol:Diethylphtalate (EtOH:DEP).

Concurrent positive control (PC) groups were included in the study to assess intra-, and inter-laboratory reproducibility and comparability. The PC groups were exposed to hexyl cinnamic aldehyde (CAS no. 101-86-0) (HCA) in doses of 5, 10 and 25 % (w/v) with 4:1 acetone:oliveoil as a vehicle. In addition, a separate vehicle control-group (VC) for the concurrent PCs was included due to different vehicles in the PC group and dose groups.

Approximately 25 µL of the preparation was applied to the dorsal surfaces of both ears. The procedure was repeated on three consecutive days (day 1-3). On day 6, three days after the last application, the mice were humanely killed. One animal in group 4 died during thymidine dosing and was excluded from the study.

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON α-METHYL-1,3-BENZODIOXOLE-5-PROPIONALDEHYDE

The available study summary includes no information of a pre-screen test nor scientific justification for the selection of the concentration series used. Further the choice of EtOH:DEP as a vehicle is a deviation from the OECD Guideline 429, of which a justification is not included in the summary.

The study method is summarized in Table 1.

Table 1: Study method

Test type	Local lymph node assay (LLNA): OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay) Performed 2005
Test substance	Test substance: α-methyl-1,3-benzodioxole-5-propionaldehyde (Helional) CAS no. 1205-17-0. EC no. 214-881-6 Vehicle: 1:3 EtOH:DEP [1] PC [2]: Substance: Hexyl cinnamic aldehyde (CAS no. 101-86-0) Conc.: 5, 10 and 25 % (w/v) preparation in acetone:olive oil (4:1)
Test animals	Mice, female (young adults) Strain: CBA/Ca Animal no. per dose: 4 [3] Weight (day 1): 16.4-20.1 g.
Administration exposure	Dose-groups: 0, 2.5, 5, 10, 25 and 50 % w/v in 1:3 EtOH:DEP [1] Control-groups: One VC[4] group and three PC[2] groups Exposure: 25 µL of the preparation was applied to the dorsal surface of the ear on day 1-3

[1] Ethanol:Diethylphthalate. [2] Positive control. [3] Animal no. 59 in group 4 died during thymidine dosing and was hence excluded from the study. [4] Vehicle control.

Results

Table 2 summarizes the result for each VC-, dose- and PC-groups in the study. The available study summary is sparse and includes no further parameters to monitor the local skin response (optional in the OECD 429).

Table 2: Study results

Test concentration (% w/v)	No. lymph nodes assays	Disintegrations per Minute	DPM per lymph node	Stimulation Index (SI)	Result
Vehicle treated control (VC)					
0 (Vehicle)	8	6458	807	N/A	-
Dose					
2.5	8	6518	815	1.0	Negative (SI < 3)
5	8	17482	2185	2.7	Negative (SI < 3)
10	8	15285	1911	2.4	Negative (SI < 3)
25	6[1]	18159	3027	3.8	Positive (SI ≥ 3)
50	8	53752	6719	8.3	Positive (SI ≥ 3)

Positive control (PC)					
Vehicle (VC(PC))	8	4397	550	N/A	-
HCA 5	8	6402	800	1.5	Negative (SI < 3)
HCA 10	8	9771	1221	2.2	Negative (SI < 3)
HCA 25	8	28921	3615	6.6	Positive (SI ≥ 3)

[1]Animal no. 59 in group 4 died during thymidine dosing and was hence excluded from the study. The Registrant evaluates the integrity of the study not to be affected by the loss of one animal in a group and the Dossier Submitter agrees with this evaluation.

All control-groups confirmed the local laboratory performance and the validity of the protocol: The VC- and the VC(PC)-groups had negative results and the PC 25 % (w/v) was positive.

The test substance caused skin sensitisation when applied in 25 and 50 % (w/v) preparations, with Stimulation Index (SI) of 3.8 and 8.3, respectively.

The Estimated Concentration needed to produce a SI of 3 (EC3) was calculated to be 16.4 % w/v (4100 µg/cm^2).

Discussion

The Registrant evaluates the study reliable without restrictions – Klimish 1 (Klimish et al. 1997).

EtOH:DEP was used as a vehicle in the dose-groups, which is a deviation from the OECD Guideline 429. Vehicles not recommended in the Guideline can be used if sufficient scientific rationale is provided. A rationale was not available in the available study summary or in the study report.

The use of EtOH:DEP as a vehicle in a LLNA assay have been discussed in relation to previous CLH proposals, e.g. citral (CAS no. 5392-40-5). In the RAC Opinion proposing harmonised classification and labelling of citral (ECHA, 2018) the use of EtOH:DEP was discussed and the vehicle was concluded to be acceptable in the conducted LLNA (ECHA, 2018). For these reasons, the Dossier Submitter evaluates the vehicle as suitable.

Conclusion

Helional was shown to be sensitising with an EC3 of 16.4 %.

3.5.2 Human data

3.5.2.1 Bennike et al., 2019

Study reference

Bennike, N.H., Zachariae, C., Johansen, J.D. Optimal patch test concentrations for three widely used sensitizing fragrance substances without mandatory labelling in cosmetics. Contact Dermatitis, 2019, 80, 325-327.

Detailed study summary and results

The objective of the study was identification of an optimal patch test concentration for three widely used sensitising fragrances including helional (CAS no. 1205-17-0), purity ≥ 98%. The study was conducted according to a protocol published by the European Society of Contact Dermatitis (ESCD).

484 consecutive dermatitis patients, aged ≥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 ≈ 100). Exclusion criteria and scoring of patch test results were conducted according to the ESCD '*Guideline for diagnostic patch testing – recommendations on best practice*'.

A starting concentration of 3.0 % (w/w) was used for patch testing helional followed by concentrations of 4.5 %, 6.8 %, 10.1 % and 15.2 %, with an occlusion time of 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. To record induced contact allergy (skin sensitisation) patients were told to contact the department if reactions occurred after final visit. In all no contact allergy (skin sensitisation) was discovered to be induced in the study and no more than a few irritant reactions were registered, which lead to an increase in all the following doses.

The patch tests were conducted by applying 20 mg of helional suspended in petrolatum (pet.) to the upper back in Finn Chambers (8mm; SmartPractice, Phoenix, Arizona), with an occlusion time of two days. Reading was performed on day 2-5 and day 7.

Table 3: Study results

Concentration (% (w/w))	Total number of patients	Positive reactions (no.)	Doubtfull reactions (no.)	Irritant reaction (no.)
3.0 %	100	0	0	0
4.5 %	104	2	0	0
6.8 %	103	1	0	0
10.1 %	100	0	0	1
15.2 % [1]	87	1	1	0

[1] Maximum allowed patch test concentration

Of the 494 patch tests performed four (0.8%, 95% confidence interval: 0.3-2.1%) had a positive reaction to helional. The authors of the study reports of clearly allergic positive patch test reactions to helional. The study resulted in recommendations of patch testing helional at 7.5 % (w/w) pet (3.0 mg/cm2).

3.6 Germ cell mutagenicity

Hazard class not assessed in this dossier

3.7 Carcinogenicity

Hazard class not assessed in this dossier

3.8 Reproductive toxicity

Hazard class not assessed in this dossier

3.9 Specific target organ toxicity – single exposure

Hazard class not assessed in this dossier

3.10 Specific target organ toxicity – repeated exposure

Hazard class not assessed in this dossier

3.11 Aspiration hazard

Hazard class not assessed in this dossier

4 ENVIRONMENTAL HAZARDS

Hazard class not assessed in this dossier

5 REFERENCES

Anonymous, 2005. Information retrived from the publicly available REACH registration dossier.

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