CLH report

Proposal for Harmonised Classification and Labelling

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

Chemical name:

Methyl oct-2-ynoate

EC Number: **203-836-6**

CAS Number: **111-12-6**

Index Number: **Not available**

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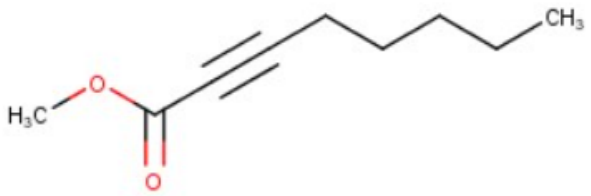
Abbreviations

^{3}HTdR	^{3}H-thymidine
ACD	Allergic Contact Dermatitis
AOO	Acetone:Olive Oil
Conc	Concentration
D	Day
DEP	Diethyl Phthalate
DS	Dossier Submitter
EtOH	Ethanol
EtOH:DEP	Ethanol: Diethyl Phthalate
EU	European Union
Exp	Exposure
HMT	Human Maximisation Test
HRIPT	Human Repeat Insult Patch Test
IFRA	International Fragrance Association
IVDK	Information Network of Departments of Dermatology - a network of departments of dermatology in germany, austria and Switzerland
LLNA	Local Lymph Node Assay
LOEL	Lowest Observed Effect Level
MEK	Methl Ethyl Ketone
NESIL	No Expected Sensitisation Induction Level
NOEL	No Observed Effect Level
PC	Positive Control
Pet	Petroleum
RIFM	Research Institute for Fragrance Materials
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers
SCCS	Scientific Committee on Consumer Safety
SCL	Specific Concentration Limit
SEQ	Sensitisation Exposure Quotient
SI	Stimulation Index
WoE	Weight of Evidence

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 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)	Methyl oct-2-ynoate*
Other names (usual name, trade name, abbreviation)	Methyl heptine carbonate Methylheptine carbonate
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	203-836-6
EC name (if available and appropriate)	-
CAS number (if available)	111-12-6
Index No.	607-RST-VW-Y
Molecular formula	C9 H14 O2
Structural formula	
SMILES notation (if available)	C(=O)(C#CCCCCC)OC
Molecular weight or molecular weight range	154.21
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Methyl oct-2-ynoate is a mono-constituent substance
Description of the manufacturing process and identity of the source (for UVCB substances only)	Methyl oct-2-ynoate is not an UVCB
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant for the entry in Annex VI

*IUCLID names according to REACH registration

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
Methyl oct-2-ynoate (mono-constituent substance)	Not publicly available – see confidential information in annex II	None	Acute Tox. 4 Skin Sens. 1 Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 3 Skin Irrit. 2 Aquatic Chronic 2 Eye Irrit. 2

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Not relevant				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Not relevant					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: **For substance with no current entry in Annex VI of CLP**

	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	607-RST-VW-Y	Methyl oct-2-ynoate	203-836-6	111-12-6	Skin Sens. 1A	H317	GHS07 Wng	H317	-	-	-

Table 5: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	Harzard classes 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	Harzard classes 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		

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance, methyl oct-2-ynoate (CAS no. 111-12-6), has no current harmonised classification in Annex VI of the CLP regulation. In total, 1757 C&L notifications have been submitted to ECHA, of which approximately 90% have classified methyl oct-2-ynoate "Skin Sens. 1" and approximately 10% have classified methyl oct-2-ynoate "Skin Sens. 1A".

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 Dosser Submitter (DS) with current self-classification

Further detail on need of action at Community level
The classification dossier is submitted according to article 36(3) and 37(1). The justification for the proposal is DS' concern about the potent sensitising properties of the substance, methyl oct-2-ynoate, and the exposure of consumers. Further DS disagrees with the current self-classification (90% of the notifiers have classified methyl oct-2-ynoate "Skin Sens. 1").

Methyl oct-2-ynoate is one of the 26 fragrances stated by the Cosmetic Regulation 1223/2009 to be listed on the ingredient label of a cosmetic product sold on the European market if the concentration is ≥ 10 ppm in leave-on products or ≥ 100 ppm in rinse-off products. The 26 fragrance substances were introduced into annex III of the Cosmetics Directive by the 7th amendment (2003/15/EC) on the basis of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) opinion (SCCNFP 1999) adopted during the plenary session of 8 december 1999. At that time there were insufficient data to allow for the determination of dose-response relationship and/or thresholds and a pragmatic administrative decision of a limit of 0.01 and 0.001% were set for rinse-off and leave-on products, respectively.

Later, SCCS (2012) described methyl oct-2-ynoate as an established contact allergen in humans, meaning there was/is sufficient human evidence present.

In the European Union (EU), toys are regulated under the Toy Safety Directive (2009/48/EC). Point 11 under Part III of Annex II to this piece of legislation regulates 66 allergenic fragrances in toys, of which methyl oct-2-ynoate is included. Directive (EU) 2020/2089 deleted methyl oct-2-ynoate (CAS 111-12-6, entry 10) as a fragrance required to be listed on the toy if its concentration was greater than 100 mg/kg. Instead methyl oct-2-ynoate is now prohibited in toys (but its presence is allowed if this is technically unavoidable under good manufacturing practice (GMP) and no more than 100 mg/kg).

Methyl oct-2-ynoate is included in one of the screening series for clinical human patch testing, namely the fragrance test series 'F-1000'. The F-1000 test series is a selection of haptens found in perfumes and beauty products.

Approximately ~ 90% of the self-classifications of methyl oct-2-ynoate have notified the substance as Skin Sens. 1 and ~10% have notified the substance as Skin Sens. 1A. A harmonised classification of methyl oct-2-ynoate as a skin sensitiser in sub-category 1A should lead to a consistent lower concentration in consumer products and thereby lower the exposure of the consumer and reduce the risk of skin sensitisation towards the substance. The classification of methyl oct-2-ynoate will lead to a generic concentration limit of ≥ 0.1% for products in which it is an ingredient.

In the SCCNFP opinion from 1999, methyl oct-2-ynoate was reported as one of 24 fragrance ingredients recognised as the most frequently recognised allergens (SCCNFP 1999). However, methyl oct-2-ynoate was reported to be less frequently reported and thus less documented as a consumer allergen compared to other

fragrance chemicals more frequently reported and well-recognised as consumer allergens. The opinion also stated that the substance is restricted to 0.01% in consumer products (IFRA guideline), due to a strong sensitising potential.

DS has scrutinised all available data on methyl oct-2-ynoate relevant to the end-point of skin sensitisation, including data from a literature search conducted in November 2021 (literature search is descriped in chapter 6). On that basis, the DS has prepared the present proposal for a harmonised classification of methyl oct-2-ynoate as Skin Sens. 1A.

5 IDENTIFIED USES

Data in the publicly available part of the REACH registration dossier for methyl oct-2-ynoate (January 2021) states that methyl oct-2-ynoate is manufacturered and/or imported to the European Economic Area in the tonnage of ≥ 10 to < 100 tonnes per annum.

The following uses are identified in the REACH registration dossier:

Registered uses of methyl oct-2-ynoate relevant for consumers include air care products, biocides (e.g. disinfectants, pest control products), perfumes and fragrances, polishes and waxes, washing & cleaning products, cosmetics and personal care products. Registered uses relevant for professionals include biocides (e.g. disinfectants, pest control products), polishes and waxes, washing & cleaning products, cosmetics and personal care products.

6 DATA SOURCES

The primary source for this dossier is a report from the Danish EPA containing a literature review of relevant studies to classify methyl oct-2-ynoate as a skin sensitiser (Bredsdorff & Nielsen, 2016). The report contains relevant literature published up to 2015.

To identify relevant literature from 2015 and forward, a literature search was conducted in November 2021.

The literature search included both scientific and other open literature. It was conducted using all identified chemical names related to the CAS no. 111-12-6 and other numerical identifiers.

Literature searches were performed using the Scientific and Technical information Network (STN) (e.g. TOXCENTER (Toxicology Center), EMBASE (Excerpta Medica), and Science Citation Index (SciSearch®).

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

7 PHYSICOCHEMICAL PROPERTIES

Table 6: 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	
Freezing point	< -50 ºC	REACH registration	Measured, OECD 102
Boiling point	219 ºC	REACH registration	Measured, OECD 103
Relative density	0.925 g/ml	REACH registration	Measured, OECD 109
Vapour pressure	10.6 Pa at 20 ºC	REACH registration	Measured, OECD 104
Surface tension	53.2 mN/m at 20 ºC	REACH registration	Measured, OECD 115
Water solubility	151 mg/L at 20 ºC	REACH registration	Measured, OECD 105
Partition coefficient	3.0 at 20 ºC	REACH registration	Measured, OECD 117

Property	Value	Reference	Comment (e.g. measured or estimated)
n-octanol/water (log Pow)			
Flash point, closed cup	96.5 °C	REACH registration	Measured, ISO 2719
Flammability	ND	REACH registration	
Explosive properties	ND	REACH registration	
Self-ignition temperature	280 ºC	REACH registration	Measured, EU Method A.15
Oxidising properties	ND	REACH registration	
Granulometry	ND	REACH registration	
Stability in organic solvents and identity of relevant degradation products	ND	REACH registration	
Dissociation constant	ND	REACH registration	
Viscosity	ND	REACH registration	

8 EVALUATION OF PHYSICAL HAZARDS

Physical hazards have not been assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Toxicokinetics have not been assessed in this dossier.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Hazard class has not been assessed in this dossier.

10.2 Acute toxicity - dermal route

Hazard class has not been assessed in this dossier.

10.3 Acute toxicity - inhalation route

Hazard class has not been assessed in this dossier.

10.4 Skin corrosion/irritation

Hazard class has not been assessed in this dossier.

10.5 Serious eye damage/eye irritation

Hazard class has not been assessed in this dossier.

10.6 Respiratory sensitisation

Hazard class has not been assessed in this dossier.

10.7 Skin sensitisation

The table below summarises relevant animal studies used to evaluate skin sensitisation for methyl oct-2-ynoate.

Table 7: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
LLNA In accordance with OECD TG 429 (2002) GLP compliant Klimisch score: 1	Mice, CBA/Ca female n = 4/dose	Methyl oct-2-ynoate in ethanol/diethylphthalate (EtOH:DEP 1:3, unit not reported)	0.05, 0.1, 0.25, 0.5, and 1% (unit not reported) Exp.: 3 days (D1-D3) ^{3}HTdR injection: D6 Sacrificed D6 (five hours after injection)	Positive EC3 = 0.45%	Unpublished report by RIFM 2006 as cited in Kern et al. 2010
LLNA In accordance with OECD TG 429 (2002) GLP compliance not stated Klimisch score: 2	Mice, no further information	Methyl oct-2-ynate in EtOH:DEP (3:1, unit not reported)	0.5, 1, 2, 5 and 10% (w/v) (It is stated that the substance should have been tested at lower concentrations)	Positive EC3 < 0.5%	Unpublished report by RIFM 2005k as cited in SCCS (2012)
Guinea pig OET (Open Epicutaneous Test); non-guideline test GLP compliance not stated Klimisch score: 4	Guinea pigs, no information on strain or sex n = 6/dose	Methyl oct-2-ynoate in ethanol (no further information)	Induction: Conc. of 1, 3, 10, 30 and 100% applied by open epicutanous administration Duration: 21 days No further information	Positive reactions at first readings: conc. 3%: 0/6 conc. 10%: 2/6 conc. 30%: 5/6 conc. 100%: 6/6	Unnamed study report (1977) as cited in REACH registration (ECHA, 2022)
GPMT No guideline stated GLP compliance not stated Klimisch score: 2 (based on the assessment by Hostynek and Maibach (2006))	Guinea pigs, no information on strain or sex n = 20/dose	No data	Three separate induction/challenge regimens Intradermal induction: 0.625%, 5% and 10% Topical induction: 1%, 3%, and 30% Challenge: 0.3%, 0.9%, and 3%	18 of 20 reactions at the least severe and middle regimens and 20 of 20 reactions at the most severe	Unpublished report by RIFM 1985d as cited in Hostynek and Maibach (2006)
Buehler test No guideline stated	Guinea pigs, no information	No data	20 guinea pigs were treated with an induction dose	14 of 20 reactions to a challenge dose	Unpublished report by RIFM 1986 as cited in

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
GLP compliance not stated Klimisch score: 2 (based on the assessment by Hostynek and Maibach (2006))	on strain or sex n = 20/dose		of 2.5%	of 5% 11 of 20 to a challenge dose of 1.5% 9 of 20 reactions at 0.5%	Hostynek and Maibach (2006)

Table 8: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations [% positive reactions]	Reference
Patch test, selected				
Diagnostic patch test Selected patients	Methylheptine carbonate 0.5% (vehicle not reported)	34 patients with contact allergy related to cosmetics were tested with 22 fragrance and flavour raw materials Region and year of patch tests not available	**3%** (1/34)	Malten et al., 1984 as cited in SCCNFP (1999)
Diagnostic patch test Selected patients	Methyl oct-2-ynoate 0.5% (vehicle not reported)	182 patients, suspected of contact allergy related to cosmetics, were tested with 22 fragrance and flavour raw materials Region and year of patch tests not available	**1.1%** (2/182)	Malten et al., 1984 as cited in SCCNFP (1999)
Diagnostic patch test Selected patients	Methyl oct-2-ynoate 0.5% in pet.	A prospective study with 320 patients, suspected of contact allergy to fragrances or cosmetics, patch tested with EU-declared fragrance chemicals (26 fragrance substances) Region: Europe (the Netherlands) Patch test conducted between: 2005-2007	**0.3%** (1/320)	Van Oosten et al. 2009
Patch test, selected - occupational settings				
Diagnostic patch test Bakers with hand eczema	Methyl heptane carbonate 0.5% in pet.	4 bakers with hand eczema were patch tested with fragrances/flavours Region and year of patch tests not available	**25%** 1 patient had a positive reaction	Malten 1979 as cited in SCCNFP (1999)
Patch test, consecutive				
Diagnostic patch test Consecutive (eczema patients)	Methyl oct-2-ynoate 2% in pet.	A retrospective study with 120 eczema patients Region: Europe (France) Patch test conducted: Year not reported	**1.67%** (2/120)	Heisterberg et al. 2010
Diagnostic patch test (eczema patients)	Methyl oct-2-ynoate 1% in pet.	A retrospective study with 1,951 eczema patients routinely tested with labelled fragrance substance and extended European baseline series Region: Europe (UK)	**0.62%** (12/1951)	Mann et al. 2014

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations [% positive reactions]	Reference
		Patch test conducted between: 2011-2012		
Diagnostic patch test (unknown consecutive patients)	Methyl oct-2-ynoate 1% (vehicle not reported)	278 patients were patch tested. No further information. Region: America Year: Not reported	**0.4%** (1/278)	Michell et al., 1982 as cited in SCCNFP (1999)
Diagnostic patch test (unknown consecutive patients)	Methyl oct-2-ynoate 1% in pet.	A retrospective study with 21,325 patients being patch tested with 26 fragrances additionally to the standard series Region: Europe (IVDK data) Patch test conducted between: 2003-2004	**0.2%** (6/2401)	Schnuch et al. 2007
Diagnostic patch test (unknown consecutive patients)	Methyl oct-2-ynoate (concentration and vehicle not reported)	A retrospective study with data from IVDK Region: Europe (IVDK data) Patch test conducted: 2007-2009	**0.16%** (n=1870)	Schnuch et al. 2015
Diagnostic patch test (patients with suspected dermatitis)	Methyl oct-2-ynate 1% in pet.	A retrospective study with 988 patients suspected of having allergic dermatitis Region: Europe (Germany) Patch test conducted between: 2005-2008	**0.1%** (1/988)	Uter et al. 2010
Diagnostic patch test (eczema patients)	Methyl oct-2-ynoate 1% in pet.	A restrospective study with 230 eczema patients Region: Europe (Denmark) Patch test conducted: 2007-2008	**0%** (0/230)	Heisterberg et al. 2010
Case studies				
Diagnostic patch test Patient with vesicular dermatitis	Methyl heptine carbonate 1% in MEK (abbreviation not stated in study report. Assumed to be an abbreviation of methyl ethyl ketone)	A 19-year-old laboratory assistant (woman) developed a localised vesicular dermatitis on her wrist following direct skin contact with methyl heptine carbonate	Very strong positive reaction at D2 and D4 (patient also positive to methyl octine carbonate)	English and Rycroft 1988
Diagnostic patch test Patient with contact dermatitis	Methyl heptane carbonate 0.5% in pet.	A 32-year-old barber (male) developed a contact dermatitis localised to the dorsa of the fingers	Positive reaction (patient also positive to hydroxycitronellal and cinnamic alcohol that together with methyl heptane carbonate were included in the cosmetic product that the barber used)	Van Ketel 1978

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations [% positive reactions]	Reference
Diagnostic patch test Patient with delayed positive reactions after patch test	Methyl oct-2-ynoate 2% in pet.	A 42-year-old woman, previously shown reaction towards deodorants, was investigated for post-surgical allergic contact dermatitis and was tested with a fragrance series	Reading at D2 and D4 showed reactions towards nickle sulphate. D16 she experienced pruritus around two erythematous, oedematous round marks on her back and a blister developed. On D37 she was systematically reviewed, and two dry erythematous round marks concurrent to the areas where methyl oct-2-ynoate and methyl octine carbonate had been tested	Heisterberg et al. 2010
Diagnostic patch test Patient with delayed positive reactions after patch test	Methyl oct-2-ynoate 1% in pet.	A 28-year old woman with facial eczema. Patch tested with the European baseline series, extended series, and fragrance series. Positive reaction to nickel sulphate and methylchloroisothiazolone/methylisothiazolinone. On D20 she was reviewed due to a late reaction. Patch test was repeated one week later.	Positive (1+) towards methyl oct-2-ynoate on D2 after re-test.	Heisterberg et al. 2010
Diagnostic patch test Patient with delayed positive reactions after patch test	Methyl oct-2-ynoate 1% in pet.	A 21-year old woman suspected of occupational hand eczema. Patch tested with European baseline series, extended series, fragrance series, and prick tested with a standard series and food series. All negative. Four weeks later she was reviewed due to a well-demarcated extremely infiltrated erythematous plaque at the area of where one of the fragrances had been tested. Patch test was repeated one week later.	Positive (2+) towards methyl oct-2-ynoate on D2 after re-test.	Heisterberg et al. 2010

Table 9: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not identified				

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

The chemical structure of methyl oct-2-ynoate indicates that it is expected to react with skin proteins directly via the Michael addition mechanism (Api el al. 2019).

Animal

The animal studies reported in 10.7.2.1 represent guideline studies as well as other studies based on testing principles that are equivalent to current test guidelines for skin sensitisation. According to the CLP criteria the results of LLNA (OECD 429), GPMT and Buehler tests (OECD 406) are directly applicable for classification and sub-categorisation of skin sensitisation.

A total of 2 LLNAs, 1 GPMT, 1 Guinea Pig OET and 1 Buehler test with methyl oct-2-ynoate have been identified.

Both LLNA studies were conducted according to OECD TG 429 (2002) and have EC3 values of < 0.5%.

The GPMT and Buehler studies are not published and have not been conducted according to a guideline. However, although the quality and reliability of these studies cannot be assessed by dossier submitter, this have been scrutinised in Hostynek and Maibach (2006). The two studies were both assessed by Hostynek and Maibach (2006), to meet all test qualification criteria (vehicle-treated and untreated controls; test concentration sufficient for response; use of appropriate vehicle; adequate compound purity; significant number of cases used). The study results are thus by dossier submitter considered as *realiable with restrictions*. In the GPMT study, 90% of the animals responded after an intradermal induction dose of 0.625% methyl oct-2-ynoate (18/20 animals showed positive reactions). Sensitisation was also observed in the Buehler test with positive reactions in 45-70% of the animals after an induction dose of 2.5% followed by challenge doses of 0.5-5%, respectively (14 out of 20 reactions to a challenge dose of 5%, 12 out of 20 to a challenge dose of 1.5%, and 9 of 20 reactions at 0.5%).

The Guinea Pig OET was not conducted using a guideline and no GLP compliance is stated. The study is not public available and the information in the REACH registration is very limited. For this reason the study cannot be assessed and the quality of the study is *not assignable*.

No relevant *in vitro* studies on methyl oct-2-ynoate (i.e. OECD TG 442C and OECD 442D) were identified in the literature.

Both LLNA studies were conducted using EtOH:DEP as vehicle, which is not listed as a recommended vehicle in the TG OECD 429, but according to the guideline, other vehicles may be used if sufficient scientific rationale is provided. EtOH containing vehicle systems are frequently used for assessing dermal effects of fragrance materials in both human and experimental studies. The use of EtOH:DEP as an alternative vehicle to acetone:olive oil (AOO) has been investigated in a comparative study, showing that EtOH:DEP is a suitable alternative vehicle to AOO in the LLNA (Betts, et al. 2007) and the vehicle is frequently used. Further the use of EtOH:DEP as a vehicle in a LLNA assay has been accepted by RAC, e.g. in the opinion on citral (CAS no. 5392-40-5).

Of the identified studies, the values from the two LLNA studies are directly applicable for classification and sub-categorisation of skin sensitisation. The remaining studies are not directly applicable for classification purposes, but support the findings of methyl oct-2-ynoate being a sensitiser.

All of the available animal studies show or support that methyl oct-2-ynoate is a skin sensitiser with a strong potency.

Human

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and is performed according to international standards by dermatologists. The results of such patch tests are usually reported as number of patients/subjects having positive reactions in relation to the total number tested, i.e. the frequency

of positive patch tests. An important factor when assessing the prevalence of positive reactions in diagnostic patch tests is how the group of patients are defined, i.e. selected patients versus consecutive/unselected patients. Selected patients can be e.g. patients with dermatitis suspected of having contact allergy to fragrances or cosmetics or special occupational groups (aimed testing). Consecutive/unselected patients are groups of patients for whom allergic contact dermatitis is generally suspected.

A total of 11 datasets with patch test data have been identified. Of these, seven includes consecutive patients (dermatitis patients), showing a frequency range of skin sensitisation of 0-1.67%. Three studies on selected patients showed positive reactions in the range of 0.3-3%, while one occupational study on selected workers showed a positive frequency of 25%. Methyl oct-2-ynoate has typically been tested in 0.5-2% pet., in the diagnostic patch tests. The total number of published cases is approximately ~ 30. Although the observed frequencies show some variations, the results confirm that positive reactions to methyl oct-2-ynoate are observed in dermatitis patients.

Five case studies are reported. A 19-year-old laboratory assistant developed a localised vesicular dermatitis on her wrist following direct skin contact with methyl heptine carbonate (methyl oct-2-ynoate). She regularly worked with methyl octine carbonate but only occasionally with methyl heptine carbonate. Patch testing showed very strong positive reactions towards both substances at day 2 and 4. The second case study was a 32-year-old barber who had developed a contact dermatitis localised to the dorsa of the fingers. The patient was patch tested and showed positive reactions to methyl heptine carbonate (0.5% in pet.), hydroxycitronellal (10% in pet.) and cinnamic alcohol (5% in pet.).

There are three case studies showing late patch test reactions (2-4 weeks), including two cases with positive re-testing. These studies show the strong potency of methyl oct-2-ynoate and are considered of very high importance to this classification proposal. The two cases showing posive re-tests of methyl 2-octynoate (methyl oct-2-ynoate) indicate that sensitisation was induced by the patch testing procedure. The clinical aspects observed in the three cases are of typical active sensitisations. An active sensitisation is defined by a negative patch test followed by a flare up after 10-20 days, and a positive reaction withing a few days after re-testing. The study by Heisterberg et al. (2010), which included patch test data from Denmark and France, concluded that the three incidences of active sensitisation observed resulted in a frequency of active sensitisation of 0.83% in the French group and 0.87% in the Danish group.

The Research Institute for Fragrance Materials (RIFM) evaluated methyl oct-2-ynoate for skin sensitization (and other non-relevant end points) in 2019 (API et al. 2019). The evaluation was based on the RIFM Criteria Document and included relevant data available at the time of writing. Based on a Weight of Evidence (WoE) approach methyl oct-2-ynoate was considered a strong skin sensitizer with a defined No Expected Sensitisation Induction Level (NESIL) of 110µg/cm^2, a NOEL-HRIPT (induction) of 118µg/cm^2 and a LOEL-HRIPT/HMT (induction) of 194 µg/cm^2.

The human studies identified are all relevant in terms of classification and confirm the sensitising properties of methyl oct-2-ynoate. Further the three cases of late patch test reactions, particularly the two cases showing posive re-tests of methyl 2-octynoate (methyl oct-2-ynoate), along with the evaluation of RIFM show the strong potency of methyl oct-2-ynoate as a skin sensitiser.

10.7.1.1 Human exposure

Methyl oct-2-ynoate is registered under REACH to be manufactured in and/or imported in a relatively low tonnage (the tonnage of $\geq$ 10 to < 100 tonnes per annum). The substance is used both by consumers and professional workers (widespread) in applications that may entail dermal exposure; e.g. in consumer products such as perfumes, cosmetics and personal care products, household and other products such as scented candles and socalled ‘air-fresheners’.

The SCCS opinion (2012) refers to a number of surveys on the presence and content in consumer products and the exposure to the consumer from products. In spite of being either not measured nor found in most of these surveys (few studies/surveys shows presence of methyl oct-2-ynoate in consumer products, such as

cosmetics and/or household products/detergents[1]), it was concluded, taking the total exposure into account, that exposure to all 26 allergenic fragrances (including methyl oct-2-ynoate) is foreseeable in daily life (survey studies cited in SCCS, 2012). However, the exposure to methyl oct-2-ynoate appears generally to be low.

In the study of Schnuch et al. (2015) methyl oct-2-ynoate was listed as a fragrance compound very rarely used, concluded on data obtained from IFRA and the German authorities (**C**hemisches und **V**eterinärunters**u**chungs**a**mt "CVUA") and 3 datasets (< 6000 products). Thus methyl oct-2-ynoate has a low labelling frequency. However, methyl oct-2-ynoate was still ranked in the top four of the 26 substances with the highest estimated sensitisation risk (SEQ) (SEQ = 400) using the IFRA data. The SEQ can be used to rank the relative risk associated with the compound. It is calculated as a quotient of the share of allergic reactions divided by the share of the exposure. This highlights that, while the substance is not used in a high tonnage, the low use/exposure may result in a relative high frequency of sensitisation.

Methyl oct-2-ynoate has previously been mentioned as a substance of which sensitisation is less frequently reported, but with a very high skin sensitising potential (SCCS 2012). The low frequency of reported cases of allergy may be linked to risk management procedures put in place by the International Fragrance Association (IFRA) more than 20 years ago. The IFRA Standards is a global risk management system for the safe use of fragrance ingredients and is a part of the IFRA Code of Practice, which is a self-regulated system of the industry, based on risk assessments conducted by an independent Expert Panel[2] for Fragrance Safety following the activities of the Research Institute for Fragrance Materials (RIFM)[3]. Standards are made and published if the Expert Panel for Fragrance Safety assess that a restriction of use is necessary for consumer and/or environmental protection (IFRA, 2020A).
For many years IFRA has had a very low standard limit of approximately 0.01% for methyl oct-2-ynoate for most categories. The last update of this standard was published in 2020 (In the 49th amendment to the IFRA code of practice) (IFRA, 2020B). The new standard limits for the finished products are shown in the table below, generally increasing the limits compared to the previous standard limits. The implementation dates for new submissions are February 2021 and for existing fragrance compounds February 2022.

TABLE 10.The IFRA standard limit for methyl oct-2-ynoate 2020.

IFRA product category	Product type that drives the category consumer exposure level (IFRA, 2020B)	IFRA standard limit
Category 1	Products applied to the lips (leave on)	0.0085%
Category 2	Products applied to the axillae (leave on)	0.0025%
Category 3	Products applied to the face/body using fingertips (leave on)	0.051%
Category 4	Products related to fine fragrance (leave on)	0.047%
CATEGORY 5	**Products applied to the face and body using the hands (palms), primarily leave-on:**	
Category 5A	Body lotion products applied to the body using the hands (palms) (primarily leave on)	0.012%
Category 5B	Face moisturizer products applied to the face using the hands (palms) (primarily leave on)	0.012%

[1] A RIVM report from 2008 showed that out of 516 consumer products, being either cosmetics or household products, methyl oct-2-ynoate was found in 1% (the content was stated on the labelling and confirmed by chemical analysis, according to (SCCS, 2012). Methyl oct-2-ynoate was also found in cosmetics/and or detergents in a german survey in 2006/2007.

[2] An international industrial group of dermatologists, pathologists, toxicologists, environmental and respiratory scientist.

[3] RIFM gather and analyze scientific data, engage in testing and evaluation, distribute information, cooperate with official agencies, and encourage uniform safety standards related to the use of fragrance substances.

IFRA product category	Product type that drives the category consumer exposure level (IFRA, 2020B)	IFRA standard limit
Category 5C	Hand cream products applied to the hands using the hands (palms) (primarily leave on)	0.012%
Category 5D	Baby Creams, baby Oils and baby talc (leave on)	0.012%
Category 6	Products with oral and lip exposure (leave on)	0.028%
CATEOGRY 7	**Products applied to the hair with some hand contact**	
Category 7A	Rinse-off products applied to the hair with some hand contact (rinse-off)	0.096%
Category 7B	Leave-on products applied to the hair with some hand contact (leave on)	0.096%
Category 8	Products with significant anogenital exposure (leave on)	0.0050%
Category 9	Products with body and hand exposure, primarily rinse off (rinse-off)	0.092%
CATEGORY 10	**Household care products with mostly hand contact:**	
Cattery 10A	Household care excluding aerosol products (excluding aerosol/spray products products)	0.33%
Category 10B	Household aerosol/spray products (Rinse-off)	0.33%
CATEGORY 11	**Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate**	
Category 11A	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure (leave on)	0.18%
Category 11B	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure (leave on)	0.18%
Category 12	Products not intended for direct skin contact, minimal or insignificant transfer to skin (non-skin contact)	No restriction

10.7.2 Comparison with the CLP criteria

Methyl oct-2-ynoate is used as a fragrance and is a well-known strong skin sensitiser. An assessment of the skin sensitising properties of methyl oct-2-ynoate has been conducted according to the current classification criteria as data are considered sufficient for sub-categorisation in this hazard class. According to CLP, Annex I, 3.4.2.2.1.3., data considered sufficient for sub-categorisation include:

"*Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitisers as described in section 3.4.2.2.2. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values*…."

According to the classification criteria sub-category 1A represent "*Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered*" (CLP table 3.4.2).

According to the classification criteria sub-category 1B represent "*Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have*

the potential to produce sensitisation in humans. Severity of reaction may also be considered" (CLP table 3.4.2).

10.7.2.1 Animal data

There are three standard animal test methods to be used when evaluating skin sensitisation for substances: the mouse local lymph node (LLNA), the guinea pig maximisation test (GPMT) and the Buehler assay.

According to the classification criteria evidence from animal studies for sub-category 1A and 1B, respectively, can include the following types of data and results (CLP tables 3.4.3 and 3.4.3):

	Animal data	
Sub-category 1A	LLNA	EC3 value ≤ 2%
	GPMT	≥ 30% responding at ≤ 0.1% intradermal induction dose or ≥60% responding at > 0.1% to ≤ 1% interdermal induction dose
	Buehler	≥ 15% responding at ≤ 0.2% topical induction dose or ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose
Sub-category 1B	LLNA	EC3 value > 2%
	GPMT	≥ 30% to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥30% responding at > 1% interdermal induction dose
	Buehler	≥ 15% to < 60% responding at > 0.2% to ≤ 20% topical induction dose or ≥ 15% responding at > 20% topical induction dose

The skin sensitisation potency in LLNA (OECD 429) is determined according to table 3.6 in the guidance on the application of the CLP criteria as shown below (ECHA, 2017).

Table 11. Skin sensitisation Potency in Mouse Local Lymph Node Assay (copied from ECHA, 2017).

EC3-value (% w/v)	**Potency**	**Predicted Sub-category**
≤ 0.2	Extreme	1A
> 0.2 - ≤ 2	Strong	1A
> 2	Moderate	1B

The skin sensitising potency in GPMT (OECD 406) is determined according to table 3.7 in the guidance on the application of the CLP criteria as shown below (ECHA, 2017).

Table 12. Potency on basis of the Guinea Pig Maximisation Test (copied from ECHA 2017)

Concentration for intradermal induction (% w/v)	**Incidence sensitised guinea pigs (%)**	**Potency**	**Predicted sub-category**
≤ 0.1	≥ 60	Extreme	1A
≤ 0.1	≥ 30 -< 60	Strong	1A
> 0.1 - ≤ 1.0	≥ 60	Strong	1A
> 0.1 - ≤ 1. 0	≥ 30 -< 60	Moderate	1B
> 1.0	≥ 30	Moderate	1B

The skin sensitising potency onbasis of a Buehler assay is determined according to table 3.8 in the guidance document on the application of the CLP criteria as shown below (ECHA, 2017).

Table 13. Potency on basis of the Buehler assay (copied from ECHA 2017)

Concentration for topical induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency	Predicted sub-category
≤ 0.2	≥ 60	Extreme	1A
≤ 0.2	≥ 15 - < 60	Strong	1A
> 0.2 - ≤ 20	≥ 60	Strong	1A
> 0.2 - ≤ 20	≥ 15 - < 60	Moderate	1B
> 20	≥ 15	Moderate	1B

Test results from the LLNA, GPMT and Buehler test can be used directly for classification. They may also be used for potency evaluation.

Both of the two identified EC3-values from LLNA studies are suitable for sub-classification. The LLNA studies; Unpublished report by RIFM 2005k as cited in SCCS (2012) and Unpublished report by RIFM 2006 as cited in Kern et al. (2010), showed EC3-values of < 0.5% and 0.45%, respectively. Both values shows a strong potency i.e. equivalent to Category 1A.

The identified GPMT (Unpublished report by RIFM 1985d as cited in Hostynek and Maibach (2006)) was conducted using three separate induction and challenge doses. The intradermal induction doses was 0.625%, 5% and 10%, leading to a positive reaction in 90-100% of the animas. In the Buehler test (unpublished report by RIFM (1986)), a induction dose of 2.5% was used, resulting in 45%, 55% and 70% positive reactions to challenge doses of 0.5%, 1.5% and 5%, respectively.

As the two studies are not conducted according to OECD 406 or available for further scrutiny, they are not applicable to sub-classification. However, the GPMT and Buehler tests support the strong potency of methyl oct-2-ynoate as a skin sensitiser.

In all, the results of the of the animal studies show a strong skin sentising potency of methyl oct-2-ynoate, supporting the classification of sub-category 1A.

10.7.2.2 Human data

According to the classification criteria for sub-category 1A and 1B, respectively, human evidence can include the following types of data (CLP section 3.4.2.2.3):

	Human data
Sub-category 1A	(a) positive response at ≤ 500 µg/cm^2 (HRIPT, HMT – induction threshold); (b) diagnostic patch test data where there is relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure; (c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis (ACD) in relation to relatively low exposure.
Sub-category 1B	(a) positive response at > 500 µg/cm^2 (HRIPT, HMT – induction threshold); (b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure. (c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis (ACD) in relation to relatively high exposure.

The Research Institute for Fragrance Materials (RIFM) evaluated methyl oct-2-ynoate for skin sensitization (and other non-relevant end points) in 2019 (API et al. 2019). Using relevant data available at the time of the assessment and a WoE approach, methyl oct-2-ynoate was considered a strong skin sensitizer with a NOEL-HRIPT (induction) of 118µg/cm and a LOEL-HRIPT/HMT (induction) of 194 µg/cm^2. According to the classification criteria in the above table, this value supports the 1A sub-categorisation of methyl oct-2-ynate.

The guidance on the application of the CLP criteria further outlines how the frequency of occurrence of skin sensitisation shall be assessed. The frequency is determined according to table 3.2 in the guidance as shown below (ECHA, 2017).

Human diagnostic patch test data	**High frequency**	**Low/moderate frequency**
General population studies	≥ 0.2%	< 0.2%
Dermatitis patients (unselected, consecutive)	≥ 1.0%	< 1.0%
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0%	< 2.0%
Workplace studies: 1: all or randomly selected workers 2) selected workers with known exposure or dermatitis	 ≥ 0.4% ≥ 1.0%	 < 0.4% < 1.0%
Number of published cases	≥ 100 cases	< 100 cases

The collected data from patch test studies thus show, compared to table 3.2 in the CLP guidance (as shown above) that

- seven identified studies with dermatitis patient (unselected, consecutive) showed a frequency range on skin sensitisation of 0-1.67%. Out of the seven studies, one study showed a high frequency (≥ 1.0 %) and six studies showed a low/moderate frequency (< 1.0 %).
- three identified studies with selected dermatitis patients (aimed testing, usually special test series) showed a frequency range of 0.3-3%, one study showed a high frequency (≥ 2.0 %) and 2 studies showed a low/moderate frequency (< 2.0 %).
- two idenfied studies with workplace studies were identified. One study was in the category of "a*ll or randomly selected workers*". This study showed a low frequency of sensitised individuls (< 0.4 %). The second study was in the category of "*selected workers with known exposure or dermatitis*" and showed a high frequency (≥ 1.0 %) (The frequency identified in the single workplace study was very high (25%), but was only based on a total of four patients).
- the number of tested dermatitis patients, showing positive reactions to methyl oct-2-ynoate, is low/moderate (<100 cases).

These findings show a low frequency of occurrence of sensitisation for methyl oct-2-ynoate in humans. However, some studies also report of a high frequency.

It cannot be established if there is an increasing or decreasing tendency in sensitised patients from the 10 identified patch test studies and one workplace study. The latest patch test data are from 2015 and a high frequency was reported in a study from 2010.

For deciding on the appropriate sub-category the data from patch test studies need to be seen in conjunction with the estimated exposure (see 10.7.1.1).

10.7.2.3 Exposure consideration

The occurrence of skin sensitisation in defined groups of patch test patients needs to be seen in conjunction with the level of exposure in order to decide on sub-categorisation of skin sensitisers. As described in a previous chapter (10.7.1.1) the exposure to methyl oct-2-ynoate from consumer products is generally considered to be low.

According to the guidance on the application of the CLP criteria an additive exposure index shall be set in order to decide on the appropriate sub-category for skin sensitisers (when based on human data). An additive exposure index of 1-4 equals to relatively low exposure, where 5-6 reflects relatively high exposure. The exposure index is determined according to table below:

Exposure data	**Relatively low exposure (weighting)**	**Relatively high exposure (weighting)**	**Score for methyl oct-2-ynoate**
Concentration/dose	< 1.0% < 500µg/cm^2 (score 0)	≥ 1.0% ≥ 500µg/cm^2 (score 2)	0
Repeated exposure	< once daily (score 1)	≥ once daily (score 2)	1
Number of exposures (irrespective of concentration of sensitiser)	< 100 exposure (score 0)	≥ 100 exposures (score 2)	2

To achieve the exposure index a response in each row in the table above is necessary. The exposure index of methyl oct-2-ynoate is estimated based on the following:

- Score 0: For the concentration/dose, based on the expected concentration (IFRA, 2020B) of methyl oct-2-ynoate in consumer products.
- Score 1: For the repeated exposure, based on SCCS estimates daily exposure (SCCS 2012): "*Quantitative analyses have revealed that the consumer is exposed to most, but not all of the 26 fragrance allergens from the use of cosmetics. However, when fragrance exposure from other consumer products, for example detergents and other household products is also taken into consideration…, exposure to all of the 26 allergens is foreseeable in daily life. Although from the data available, the exposure to α-amylcinnamyl alcohol, cinnamal, methyl-2-octynoate, Evernia prunastri (oak moss) and tree moss may appear to be low, these are very strong allergens*." (SCCS, 2012, page 79)
- Score 2: For number of exposure based on anticipated exposure of sensitised individuals to methyl oct-2-ynoate at least more than 100 times. Methyl oct-2-ynoate is a substance of which a daily exposure of the consumer is not expected. However, SCCS still foresee exposure in daily life (SCCS, 2012) and numbers of exposure can be expected to be above 100 exposures.

  An additive exposure index of maximum 4 (0+2+2) has been set, thus indicating relatively low exposure. A decision on the appropriate sub-category for skin sensitisers based on human data is assessed according to table 3.4 in the guidance on the application of the CLP criteria, below.

Exposure data	**Relatively low frequency of occurrence of skin sensitisation**	**Relatively high frequency of occurrence of skin sensitisation**
Relatively high exposure (score 5-6)	Sub-category 1B	Category 1 or case by case evaluation
Relatively low exposure (score 1-4)	**Category 1 or case by case evaluation**	Sub-category 1A

Based on the human data showing a relatively low exposure and a relatively low frequency of occurrence of skin sensitisation, classification of methyl oct-2-ynoate should be category 1 or case by case evaluation. Due to the high potency of methyl oct-2-ynoate, shown in the LLNA studies, a Category 1 is not acceptable for the substance and argumentation of the relevant category is discussed using a Weight of Evidence approach in the following chapter.

10.7.2.4 Weight of Evidence

Both animal and human data, documenting the skin sensitising properties of methyl oct-2-ynoate, have been identified and described in the present dossier. These data are considered in a total weight of evidence assessment (WoE) according to the CLP criteria, Annex I: 3.4.2.2.4.

The animal data identified and described in this classification dossier provides evidence of a strong sensitising effects of methyl oct-2-ynoate. This is primarily based on the two LLNA studies, conducted according to OECD TG 429 with EC3 values < 0.5%. The LLNA studies thus shows a strong potency i.e. equivalent to Category 1A.

As both the identified GPMT study and the Buthler test were not conducted according to OECD TG nor available for further scrutiny, they are not applicable to sub-classification. However, the GPMT and Buehler test supports the strong potency of methyl oct-2-ynoate as a skin sensitiser.

The animal studies identified thus indicate a sub-categorisation of category 1A.

Human patch test data provides evidence of a low frequency of sensitisation for methyl oct-2-ynoate in humans (latest 2015). Diagnostic patch test data obtained from dermatitis patients attending individual dermatology clinics or collected clinical data is the primary source of clinical information on the occurrence of skin sensitisation (ECHA, 2017) and diagnostic patch tests are generally performed under internationally standardised conditions. The human patch test data reported in this dossier consist primarily of data from Europe.

A total of 11 datasets with patch test data, five case studies and three case studies showing late patch test reactions (2-4 weeks) were identified (7 with consecutive patiens, a frequency range of 0-1.67% ; 3 with selected patiens, frequency range of 0.3-3% ; 1 occupational study on selected workers, frequency of 25%). Although the observed frequencies in the patch tests show some variations, the results confirm that positive reactions to methyl oct-2-ynoate are observed in dermatitis patients. Further, the three case studies showing late patch test reactions (2-4 weeks), including two cases with positive re-testing, indicates active sensitisation and thus shows the strong potency of methyl oct-2-ynoate and are considered of very high importance to this classification proposal.

The relatively low frequency of occurrence of skin sensitisation and the relatively low exposure, categorises methyl oct-2-ynoate in "*category 1 or case by case evaluation".*

Based on a Weight of Evidence (WoE) approach, RIFM evaluated methyl oct-2-ynoate to be a strong skin sensitizer with a defined No Expected Sensitisation Induction Level (NESIL) of 110µg/cm2, a No Observed Effect Level with Human Repeat Insult Patch Test (NOEL-HRIPT) (induction) of 118µg/cm and a LOEL-HRIPT/Human Maximisation Test (HMT) (induction) of 194 µg/cm2 (API et al. 2019). With a positive response ≤ 500 µg/cm2 (HRIPT, HMT – induction threshold), the HRIPT values in Api et al. (2019) supports a sub-categorisation of category 1A.

Methyl oct-2-ynoate is known as an established skin sensitiser, with a special concern due to the strong potency of skin sensitisation. Although it is foreseeable that consumers are exposed to the substance in daily life, the overall exposure to methyl oct-2-ynoate is estimated to be relatively low based on information on the use in consumer products and the IFRA restriction in the last two decades (see chapter 10.7.1.1). However, sensitisation is still observed in patch test - which is excpected to be observed due to its strong potency. The strong potency observed in the two LLNA studies and further supported by the three case studies indicating active sensitisation at 1 or 2% in pet.

Based on the the high potency of skin sensitisation observed in the two LLNAs and the three case studies indicating active sensitisation at 1 or 2% in petrolatum, combined with occurrence of human cases despite the relatively low exposure of consumers, a classification of methyl oct-2-ynoate as a strong sensitiser in sub-category 1A is justified.

10.7.3 Conclusion on classification and labelling for skin sensitisation

The available animal and human studies confirm the strong sensitising properties of methyl oct-2-ynoate. The focus of the current dossier is the sensitising potency of methyl oct-2-ynoate, which is most clearly reflected from the animal data (LLNA) and further supported by registered case studies of active sensitisation in humans.

Based on the low EC3 values from the available LLNA studies, showing the strong potency of the substance to cause skin sensitisation, supported by the human data, a classification of methyl oct-2-ynoate as a strong skin sensitiser with Skin sens. 1A; H317: May cause an allergic skin reaction, is proposed.

No scientific information has been identified to set a specific concentration limit (SCL) and the generic concentration limits of the sub-category 1A (0.1% w/v) should be used.

10.8 Germ cell mutagenicity

Hazard class has not been assessed in this dossier.

10.9 Carcinogenicity

Hazard class has not been assessed in this dossier.

10.10 Reproductive toxicity

Hazard class has not been assessed in this dossier.

10.11 Specific target organ toxicity-single exposure

Hazard class has not been assessed in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Hazard class has not been assessed in this dossier.

10.13 Aspiration hazard

Hazard class has not been assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Hazard classes have not been assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Hazard classes have not been assessed in this dossier.

13 ADDITIONAL LABELLING

Skin sensitisers, sub-category 1A, has the generic concentration limit triggering classification of a mixture of ≥ 0.1%. 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 ≥ 0.01% of a skin sensitiser in category 1A should be subject to the specific labelling requirements of section 2.8 of Annex II.

A mixture containing ≥ 0.01% methyl oct-2-ynoate should therefore use the statement:

EUH208 – 'Contains methyl oct-2-ynoate. May produce an allergic reaction'

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15 ANNEXES

Annex I: detailed study summaries

Annex II: confidential information