Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

(3*E*)-dec-3-en-2-one

EC Number: -
CAS Number: 18402-84-1

CLH-O-0000007098-68-01/F

Adopted

18 March 2022

18 March 2022

CLH-O-0000007098-68-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **(3*E*)-dec-3-en-2-one**

EC Number: **-**

CAS Number: **18402-84-1**

The proposal was submitted by the **Netherlands** and received by RAC on **3 May 2021.**

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

PROCESS FOR ADOPTION OF THE OPINION

Netherlands has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **7 June 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **6 August 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Peter Hammer Sørensen**

Co-Rapporteur, appointed by RAC: **Raili Moldov**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **18 March 2022** by **consensus.**

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

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	(3*E*)-dec-3-en-2-one	-	18402-84-1	Acute Tox. 4 Asp. Tox. 1 Skin Irrit. 2 Skin Sens. 1 Aquatic Chronic 2	H332 H304 H315 H317 H411	GHS07 GHS08 GHS09 Dgr	H332 H304 H315 H317 H411	EUH071	inhalation: ATE = 1.5 mg/L (dusts or mists)	
RAC opinion	TBD	(3*E*)-dec-3-en-2-one	-	18402-84-1	Acute Tox. 4 Asp. Tox. 1 Skin Irrit. 2 Aquatic Chronic 2	H332 H304 H315 H411	GHS07 GHS08 GHS09 Dgr	H332 H304 H315 H411	EUH071	inhalation: ATE = 1.5 mg/L (dusts or mists)	
Resulting Annex VI entry if agreed by COM	TBD	(3*E*)-dec-3-en-2-one	-	18402-84-1	Acute Tox. 4 Asp. Tox. 1 Skin Irrit. 2 Aquatic Chronic 2	H332 H304 H315 H411	GHS07 GHS08 GHS09 Dgr	H332 H304 H315 H411	EUH071	inhalation: ATE = 1.5 mg/L (dusts or mists)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

(3*E*)-3-decen-2-one is intended to be used as plant growth regulator in potatoes during storage. The product is applied by hot fogging.

(3*E*)-3-decen-2-one has not been previously classified by RAC or TC C&L. (3*E*)-3-decen-2-one has been registered under REACH. The studies in the REACH registration dossier appear to be the same as those that were submitted for the active substance approval under Regulation (EC) No 1107/2009 (PPP Regulation).

A Draft Assessment Report (DAR) and Proposed Decision of the Netherlands has been prepared in the context of the possible approval of (3*E*)-3-decen-2-one under the PPP Regulation.

During the drafting of the DAR and the CLH proposal it became clear that the active substance actually placed on the market is the E-enantiomer with only a minor fraction of the Z-enantiomer. Therefore, the identity of the substance in this CLH proposal is limited to this enantiomer.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Explosive

No decomposition or breakdown was observed (peak at 226.28 °C with 271.106 J/g) at up to 400 °C (Benton, 2011). (3*E*)-dec-3-en-2-one is not considered to be explosive (Neumans, 2011); the structure of the substance also corroborates this. Hence, no classification was proposed.

Flammable liquid

In a study (EC A.9), the flash point of the liquid is determined to be 99 °C (> 60 °C). The criteria for classification as a flammable liquid are not met and no classification was proposed.

Self-reactive substance or mixture

No test data presented. The available physical-chemical information and the structure of the substance indicates no self-reacting properties; thus, no classification was proposed.

Pyrophoric liquid

No specific studies are available. However, no indication of pyrophoric properties is demonstrated based on the flashpoint (99 °C) and self-ignition temperature (275 °C). Hence the classification procedure has not been applied.

Self-heating substance or mixture

A study conducted in accordance with EC A.15 is available (Benton, 2011). In this study, the self-ignition temperature of the liquid is determined to be 275 °C. No classification was proposed.

Oxidising liquid

(3*E*)-dec-3-en-2-one is not considered to have oxidising properties (Neumans, 2011); the structure of the substance also corroborates this. Hence, no classification was proposed.

Substance or mixture corrosive to metals

No specific test data available. Based on the structure of (3*E*)-dec-3-en-2-one (aliphatic ketone) the substance is not considered to be corrosive to metals. A 1 % dilution has a pH of 4.33, which does not indicate corrosive properties. Thus, no classification was proposed.

Comments received during consultation

One Company-Manufacturer commented and agreed to propose no classification for any of the physical hazards.

Assessment and comparison with the classification criteria

Explosive

The dossier submitter (DS) proposed no classification based on expert judgement relying on the structure of the substance and the lack of observation of decomposition or breakdown at up to 400 °C. RAC notes that the exothermic decomposition energy is below 500 °C; hence, no classification is applicable.

Flammable liquid

The DS presented data on the determined flash point of 99 °C. RAC agrees with the DS that data are conclusive and that classification is not warranted.

Self-reactive substance or mixture

RAC notes that no specific test data are available. RAC agrees with the DS that classification is not warranted based on the decomposition data and the structure of the substance.

Pyrophoric liquid

RAC notes that no specific test data are available. RAC agrees with the DS to not classify (3*E*)-dec-3-en-2-one into the pyrophoric liquid category based on flash point (99 °C) and self-ignition temperature (275 °C) as this shows no potential to ignite spontaneously on coming into contact with air.

Self-heating substance or mixture

RAC agrees with the DS that classification is not warranted based on the determined self-ignition temperature of 275 °C.

Oxidising liquid

The DS proposed no classification based on expert judgement relying on the structure of the substance. RAC agrees with the DS proposal for no classification as the classification procedure for this hazard class shall not apply.

Substance or mixture corrosive to metals

RAC notes that no specific test data is available. However, RAC agrees with the DS that classification is not warranted based on the structure of the substance and the low pH of the dilution solution.

Overall, RAC agrees with the rationale of the DS and that **no classification and labelling for the physical hazards is warranted for (3*E*)-dec-3-en-2-one**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

ACUTE ORAL TOXICITY

Summary of the Dossier Submitter's proposal

Based on data for acute oral toxicity with an oral LD_{50} value higher than 5000 mg/kg bw in the rat, the DS proposed no classification for acute oral toxicity.

Comments received during consultation

One comment supporting the proposal was received from a Member State Competent Authority (MSCA).

Assessment and comparison with the classification criteria

***Table**: Summary table of animal study on acute oral toxicity*

Method, guideline	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD TG 425	Rat, Sprague-Dawley, females, 4/dose	(3*E*)-3-decen-2-one purity 98.57 %	Single dose, gavage at 5000 mg/kg bw	> 5000 mg/kg bw	CA 5.2.1-01, 2009a

In an acute oral toxicity study, 4 females were treated with a single gavage dose of (3*E*)-3-decen-2-one at a dose level of 5000 mg/kg bw. The study was carried out in accordance with OECD TG 425.

One out of 4 females died on day 2 of the study. Hypoactivity, anogenital staining, hunched posture and soft faeces were observed. In the surviving animals, clinical signs consisted of anogenital staining, hypoactivity with hunched posture, piloerection, reduced faecal volume, soft faeces and facial stains in all animals. The animals were fully recovered by day 6. No effect on bodyweight occurred. Red intestines were observed in the animal that died.

Based on the result of the study with an acute oral LD_{50} was > 5000 mg/kg bw, RAC agrees with the DS that **no classification for acute oral toxicity is warranted**.

ACUTE DERMAL TOXICITY

Summary of the Dossier Submitter's proposal

Based on data for acute dermal toxicity with a dermal LD_{50} value higher than 5000 mg/kg bw in the rat, the DS proposed no classification for acute dermal toxicity.

Comments received during consultation

Support for the DS proposal was received from one MSCA.

Assessment and comparison with the classification criteria

***Table**: Summary table of animal study on acute dermal toxicity*

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Value LD_{50}	Reference
OECD TG 402	Rat, Sprague-Dawley, males and females, 5/sex/dose	(3*E*)-3-decen-2-one purity 98.57 %	5000 mg/kg bw, 24 hours (semi-occlusive)	> 5000 mg/kg bw	CA 5.2.2-01, 2009

In an acute dermal toxicity study, groups of 5 male and 5 females were treated with a single topical application of (3*E*)-3-decen-2-one at a dose level of 5000 mg/kg bw for 24 hours. The study was carried out in accordance with OECD TG 402. The animals were observed for mortality, signs of gross toxicity and behavioural changes at least once daily for up to 14 days. Body weights were recorded prior to application and again on days 7 and 14 (termination) or after death. Necropsies were performed on all animals.

One out of 5 females died on day 2 of the study, no mortality occurred in males. In the female that died, hypoactivity and prone posture were observed. In the surviving animals, clinical signs consisted of hypoactivity (recovered by day 2), and dermal irritation in all animals (between days 1 and 14). No effect on body weight occurred. Extremely red intestines were observed in the female that died during the study.

Based on the result for acute dermal toxicity with an LD_{50} > 5000 mg/kg bw, RAC agrees with the DS that **no classification for acute dermal toxicity is warranted**.

ACUTE INHALATION TOXICITY

Summary of the Dossier Submitter's proposal

The acute inhalation LC_{50} of the test substance was found to be between 0.52 and 2.04 mg/L for male rats and > 2.04 mg/L for female rats. Given the incidence of mortality at these dose levels, it is apparent that the LC_{50} in males is close to 2 mg/L and > 1 mg/L.

Based on the LC_{50} value of > 1 mg/L, the DS proposed classification as Acute Tox. 4; H332 for (3*E*)-3-decen-2-one. As no LC_{50} could be estimated, the DS proposed to apply the converted acute toxicity estimate (ATE) of 1.5 mg/L (dusts or mists) as included in table 3.1.2 in Annex I of CLP.

For substances classified for acute inhalation toxicity and for which the available data indicates that the mechanism of toxicity is corrosivity, labelling with EUH071 'Corrosive to the respiratory tract' is required (CLP 3.1.2.3.2). Given the clear macroscopic changes of the lungs in the dead rats in the acute inhalation study (lung oedema and discoloration), and the presence of erosion and ulceration of the respiratory tract in the 5-day inhalation study, this additional label is considered justified by the DS.

Comments received during consultation

One MSCA supported the proposal, and they also proposed to use the geometric mean for estimating an approximate LC_{50}. The geometric mean would be somewhere around 1.7 mg/L which is close to the ATE of 1.5 mg/L and therefore is well supported. The company-manufacturer agreed with the proposed classification and the selection of the ATE of 1.5 mg/L. They, however, did not agree with the proposed additional EUH071 labelling "Corrosive to the respiratory tract"

as the mechanism of toxicity is irritation and not corrosivity. Additionally, the substance is classified as Skin Irrit. 2 and not as corrosive to skin and has no classification for eye irritation.

Assessment and comparison with the classification criteria

***Table**: Summary table of animal study on acute inhalation toxicity*

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value LC_{50}**
OECD TG 403 Deviation: strain not reported	Rat, males and females, 5/sex/dose	(3*E*)-3-decen-2-one purity 98.57 % MMAD: 2.6 µm and 2.95 µm	0.52 and 2.04 mg/L, 4 hours (nose-only)	LC_{50} male > 1 mg/L LC_{50} female > 2.04 mg/L

In an acute inhalation study, groups of five male and five female rats were exposed to 0.52 mg/L or 2.04 mg/L (3*E*)-3-decen-2-one for 4 hours, nose-only exposure (mist, MMAD of 2.6 and 2.95 µm at 0.52 and 2.04 mg/L, respectively). The study was carried out in accordance with OECD TG 403 with the deviation that the strain was not reported.

Details on mortality are reported in the table below.

***Table**: Summary of mortality*

Dose (mg/L)	**Males**	**Females**	**Combined**
0.52	1/5	-	1/5
2.04	3/5	0/5	3/10

At 0.52 mg/L, the observed clinical signs included hypoactivity, irregular respiration and moist rales, hunched posture, reduced faecal volume, facial and/or anogenital staining in males. At 2.04 mg/L, clinical signs included hypoactivity, abnormal respiration, hunched posture, reduced faecal volume, nasal and oral discharge and/or facial staining. Three animals lost weight by day 7. Oedema and discolouration of the lungs, discolouration of the liver and yellow distended intestines in males were also seen. In females no gross abnormalities were observed.

The acute inhalation LC_{50} of the test substance was found to be between 0.52 and 2.04 mg/L for male rats and > 2.04 mg/L for female rats.

Given the incidences of mortality at these dose levels, RAC estimates that the LC_{50} value in males is close to 2 mg/L and > 1 mg/L which would warrant an Acute Tox. 4 classification. RAC also agrees with the DS and the commenting MSCA to use the converted ATE of 1.5 mg/L (dusts or mists).

At the dose of 0.52 mg/L, extremely red lungs were reported in one male, and at 2.04 mg/L red oedematous lungs were reported in 2 males and dark red extremely oedematous lungs in one additional male. In the 5-day inhalation toxicity study, degeneration, erosion and ulceration of several tissues were reported in animals exposed at 0.531 mg/L and also 0.278 mg/L.

Since data indicate that the mechanism of toxicity is corrosivity, as lung oedema and discoloration of lungs of dead animals and erosion and ulceration of the respiratory tract in the inhalation study were observed, labelling with EUH071 "corrosive to the respiratory tract" is required (CLP 3.1.2.3.2).

Consequently, RAC considers **classification of (3*E*)-3-decen-2-one as Acute Tox. 4; H332, with an ATE of 1.5 mg/L (dusts or mists) and the additional labelling with EUH071, warranted**.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The DS proposed no classification based on the information from the acute oral and dermal studies. The respiratory irritation observed in the acute inhalation study would warrant classification with STOT SE; however, this would be an additional classification as the substance is classified for acute inhalation toxicity. Moreover, the addition of the label EUH071 was proposed.

Comments received during consultation

Comments agreeing with the DS proposal were received from one Company-Manufacturer and one MSCA.

Assessment and comparison with the classification criteria

According to the CLP Regulation, substances should be classified for STOT SE when:

- They produce significant toxicity in animals (relevant for humans) or humans following single exposure at certain dose levels: Cat. 1
- They have the potential to be harmful to animals (relevant for humans) or humans following single exposure at certain dose levels: Cat. 2
- They have transient narcotic effects or cause transient respiratory tract irritation: Cat. 3

(3*E*)-3-decen-2-one does not fulfil these criteria as the effects observed at 5000 mg/kg bw in the acute oral and dermal studies were limited and seen above 2000 mg/kg bw. In the *in vivo* Comet assay, clinical signs, including salivation, flattened posture, decreased activity, unsteady gait, chin rubbing, and piloerection were observed at 1000 and 2000 mg/kg bw. However, these do not represent significant or specific toxicity and are not considered to be sufficient for classification.

The respiratory irritation observed in the acute inhalation study would warrant classification with STOT SE. However, this would be a double classification as the substance is already classified for acute inhalation toxicity and the label EUH071 is proposed.

Therefore, RAC concludes that **no classification is warranted for STOT SE, in line with the DS proposal**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS proposed classification as Skin Irrit. 2; H315, based on results from an OECD TG 404 in rabbits. A mean value of ≥ 2.3-≤ 4.0 for erythema/eschar or oedema in at least 2 out of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal were observed.

Comments received during consultation

Support was received for the DS proposal by one Company-Manufacture and one MSCA, which also proposed to include the additional pictogram GHS05.

Assessment and comparison with the classification criteria

Two OECD guideline studies were included in the CLH dossier, one in rabbits and one in rats. A summary is presented below:

***Table**: Summary of skin irritation studies*

Method, guideline	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results -Observations and time point of onset -Mean scores/animal -Reversibility**
OECD TG 404	Rabbit, New-Zealand White, males, 3/dose	(3*E*)-3-decen-2-one purity 98.57 %	0.5 mL, 4 hours (semi-occlusive)	Erythema (grade 1-4) from 0.5 hours after treatment. Oedema (grade 1-3) from 0.5 hour after treatment Mean score erythema: 3.2 Mean score oedema: 2.1 Reversible by day 14
OECD TG 402	Rat, Sprague-Dawley, males and females, 5/sex/dose	(3*E*)-3-decen-2-one purity 98.57 %	5000 mg/kg bw, 24 hours (semi-occlusive)	Erythema in 4/5 males and 4/5 females Desquamation 5/5 males and 3/5 females Reversible by day 14 in all animals except one male which had desquamation until day 14

In a skin irritation study, 3 male New-Zealand White rabbits were treated with 0.5 mL (3*E*)-3-decen-2-one for 4 hours under semi-occlusive dressing. The study was carried out in accordance with OECD TG 404. The animals were observed and scored for skin irritation according to Draize at 30-60 minutes, 24, 48 and 72 hours and at 7, 10 and 14 days after patch removal. Animals were observed for signs of gross toxicity and behavioural changes at least once daily during the test period.

The primary irritation scores are summarised in the table below.

*Table**: Summary of results for primary skin irritation***

Scores observed after	**0.5 hour**	**24 hrs**	**48 hrs**	**72 hrs**	**7 days**	**10 days**	**14 days**	**Mean score 24-72 hrs**
Erythema	2, 3, 4	2, 3, 4	3, 3, 4	3, 3, 4	2, 2, 3	1, 0, 1	0, 0, 0	2.7, 3.0, 4.0
Oedema	3, 3, 3	2, 3, 2	2, 2, 2	2, 2, 2	1, 1, 1	0, 0, 1	0, 0, 0	2.0, 2.3, 2.0

According to Regulation (EC) No 1272/2008 (CLP Regulation) Table 3.2.2, a substance should be classified for skin irritation in Category 2 if it fulfils the following criteria:

(1) Mean value of ≥ 2.3-≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or

(2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or

(3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

Since (3*E*)-3-decen-2-one resulted in a mean erythema score above 2.3 in all three animals in the skin irritation study in rabbits, RAC concludes that **(3*E*)-3-decen-2-one warrants classification as Skin Irrit. 2; H315**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for serious eye damage/irritation. Based on an OECD TG 405 study in rabbits, the mean score was < 1 in all animals for corneal opacity and iritis, and < 2 for conjunctival redness and chemosis. Further, all effects were reversible within 10 days.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

Summary of the submitted study on eye damage/irritation:

***Table**: Summary of the submitted study on eye damage/irritation*

Method, guideline	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results** **- Observations and time point of onset** **- Mean scores/animal** **- Reversibility**
OECD TG 405	Rabbit, New-Zealand White, females, 3/dose	(3*E*)-3-decen-2-one purity 98.57 %	0.1 mL	Mean score corneal opacity: 0.1 Mean score iritis: 0 Mean score conjunctival redness: 1.4 Mean score conjunctival chemosis: 0 Reversible by day 10

In an eye irritation study, 3 female New-Zealand White rabbits were treated with 0.1 mL (3*E*)-3-decen-2-one in the conjunctival sac. The left eye remained untreated and served as a control. Ocular irritation was evaluated according to Draize at 1, 24, 48 and 72 hours and at 4, 7, and/or 10 days post instillation. At 24 hours, a fluorescein dye evaluation procedure was used to verify the absence of corneal damage. Observations for signs of gross toxicity and behavioural changes were made at least once daily during the test period.

According to CLP Regulation Table 3.3.2.1.2, a substance should be classified for eye irritation in category 2 if it fulfils the following criteria:

Substances that produce in at least in 2 of 3 tested animals, a positive response of:

(a) corneal opacity ≥ 1 and/or

(b) iritis ≥ 1, and/or

(c) conjunctival redness ≥ 2 and/or

(d) conjunctival oedema (chemosis) ≥ 2

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

In line with the DS proposal, RAC concludes that **no classification for serious eye damage/irritation is warranted** since the mean score was < 1 in all animals for corneal opacity and iritis, and < 2 for conjunctival redness and chemosis. Further, all effects were reversible within 10 days.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed classification as Skin Sens. 1 for (3*E*)-3-decen-2-one, based on the results of a Buehler study and on information from similar substances that were collected to assess the possibilities for grouping and read-across.

In their assessment of the Buehler study, performed according to OECD TG 406 on Guinea pigs, the DS concluded that the reactions seen in the study were not clear and as such do not allow a conclusion regarding the skin sensitising properties of this substance.

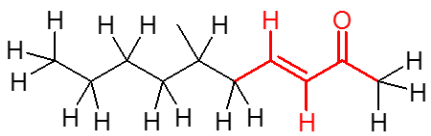
(3*E*)-3-decen-2-one is an alpha,beta-unsaturated ketone that interacts with skin proteins via Michael addition mechanism. All substances with a high structural similarity are known to induce skin sensitisation. The skin sensitisation prediction made by the DS using the DEREK database is based on the presence of the following, mechanistically based structural alert in the structure:

Alert 480: alpha,beta-unsaturated ketone or precursor.

This alert describes the skin sensitisation potential of alpha,beta-unsaturated ketones and precursors which interact with skin proteins via a Michael addition mechanism.

The presence of a skin sensitisation structural alert within a molecule indicates that the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend on its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation. It should be noted that (3*E*)-3-decen-2-one can be considered, in terms of $\log K_{ow}$, $\log K_p$, molecular weight, solubility, a substance with a good bioavailability, which is expected to be absorbed into the skin sufficiently to be able to cause skin sensitisation effects.

The place of the alert in (3*E*)-3-decen-2-one is shown in the structure representation below, where also the hydrogen atoms are indicated:



Comments received during consultation

One Company-Manufacturer did not agree with the use of read-across in this case. They stated that despite the very faint erythema scored as 0.5, the Buehler test should be considered negative as supported by a statement from the study director; thus, the substance has no potential for sensitisation.

One MSCA supported the use of read across and the use of the DEREK prediction (substance is a PLAUSIBLE skin sensitiser) and support the conclusion by the DS.

Assessment and comparison with the classification criteria

One OECD TG 406, Buehler test, was included in the CLH dossier with the following results.

Table: Summary of the submitted Buehler test

Method, guideline	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results**
OECD TG 406, Buehler test	Guinea pig, Hartley albino	(3*E*)-3-decen-2-one purity 98.57 %	100 % first four inductions 75 % remaining inductions Three times a week for 3 weeks 1 % challenge, 27 days after first induction (in mineral oil)	Topical induction caused very faint to moderate erythema (0.5-2), following challenge very faint erythema (0.5) was noted.

In a skin sensitisation study, a group of 20 male and female Guinea pigs were treated with 9 topical inductions and 1 topical challenge of (3*E*)-3-decen-2-one. An additional group of 10 animals served as control. For the first four inductions, 100 % w/w of the test material was used while a 75 % w/w mixture was used for the remaining challenges. Twenty-seven days after the first induction dose, a challenge dose of the test substance at its highest non-irritating concentration (1 % w/w mixture in mineral oil) was applied to a naïve site on each Guinea pig. The doses were based on the results of a range-finding study. Approximately 24 hours and 48 hours after each induction and challenge dose, the animals were scored for erythema.

Topical induction caused very faint to moderate erythema (0.5-2). Following challenge with 1 % w/w, very faint erythema (0.5) was noted for seven of twenty sites 24 hours after challenge.

***Table**: Results of the challenges*

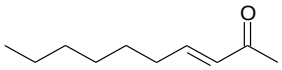
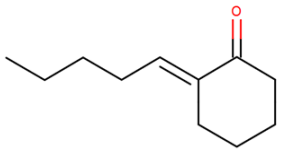
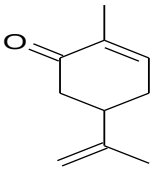
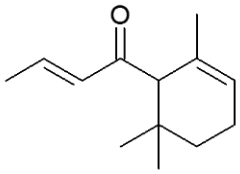
	Incidence of positive response	
	Hours	
	24	**48**
Test animals	7/20 (severity 0.5)	1/20 (severity 0.5)
Naïve control animals	1/10 (severity 0.5)	0/10

Similar irritation persisted at one site through 48 hours. The very faint erythema (score 0.5) was not considered a positive reaction by the study authors. However, an increase in this score was observed in the treatment group compared to control. Furthermore, the score of 0.5 is not in line with OECD TG 406 which requires either a score of 0, 1, 2 or 3. Therefore, no clear conclusion can be drawn from this study on the skin sensitising properties.

Since no clear conclusion could be drawn on the basis of the study, a read-across analysis was carried out.

Read Across approach by the DEREK database

***Table**: Results of the DEREK prediction and structure of the analogues*

Name of the substance	Structural	$LogK_{ow}$ / $logK_p$	Results
Substance to be evaluated (3*E*)-3-decen-2-one		3.16 / 1.42	DEREK; Plausible
2-pentylidene cyclohexanone		5.06 / -0.41	Strong Sensitisation results in human maximization test
Carvone		2.2 / -2.07	Skin Sens. 1 in GPMT
Damascone		3.83 / -1.18	Strong sensitiser in GPMT

This prediction made by using DEREK database, is based on the presence of alpha,beta-unsaturated ketone structural alert in the structure.

This alert describes the skin sensitisation potential of alpha,beta-unsaturated ketones and precursors which interact with skin proteins via a Michael addition mechanism.

Read Across approach by QSAR, VEGA-CEASAR and VEGA-IRFMN/JRC

(3*E*)-3-decen-2-one is predicted positive for skin sensitisation potential via Michael addition in QSAR Toolbox (within applicability domain). In the VEGA–(CEASAR) databases, the substance falls within the applicability domain and the model gives a positive prediction which is, however, based on data from aldehydes. The PRED SKIN provided positive skin sensitisation potential for AOP key events, including LLNA, DPRA, Keratinocyte responses and h-LCAT. However, the prediction for human maximization test and HRIPT were negative.

Assessment and conclusion by RAC

The only available study is a Buehler Guinea pigs study that shows reactions with grading 0.5. There are no human data available either. In their proposal for skin sensitisation, the DS referred to the specific consideration in the CLP Regulation, Annex I 3.4.2.2.4.3: if a combination of two or more of the listed indicators is positive, classification could be applied based on a case-by-case basis. In the DS assessment, indicator e) (positive results from close structural analogues) is fulfilled as close analogues are positive. In addition, indicator c) (data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in section 3.4.2.2.3, but which are sufficiently close to the limit to be considered significant) is also considered as fulfilled based on the response in the Buehler test of 0.5 (grading scale), which is not considered positive but sufficiently close to the limit of a positive result (a grading scale of 1). The other three indicators are not met as there is no human data or information from non-standard tests.

The only available study for assessing the skin sensitisation potential is a Buehler Guinea pig study. The study director stated in a separate position paper, that the result of the Buehler test is negative, and the substance should not be classified as a skin sensitiser, despite the increased incidence of the 0.5 scores seen in the test animals compared to the controls. Although such increased incidence may indicate a too low concentration chosen for the challenge, the concentration of 1 % used by the study director is considered justified, based on the results of the preliminary irritation study.

RAC agrees that reactions of grade 0.5 in dermal sensitisation studies does not necessarily mean that they are positive for sensitising potential. There is no equivalent grading of 0.5 in the OECD TG 406 and it is important to note that there is no consensus that such responses are directly equivalent to an OECD TG 406 grade 1 scored reaction. Buehler (1994) discussed the scoring system in a 1994 paper and noted that the most controversial aspect was the 0.5 grade for patchy erythema. According to Buehler "this designation covers a wide range of slight reactions from an effect due to hydration to a more substantive erythema that is still patchy". Buehler only considered grades 1, 2 and 3 to be indicative of a clear positive response.

Buehler (1994) noted that in cases where experimental results were not clear a rechallenge would be necessary. If any one of the test animals showed greater reactivity at rechallenge, then the test material could be designated as a sensitiser.

Unfortunately, a rechallenge was not performed in this case. RAC considers that a score of 0.5 therefore seems to imply a doubtful/negligible erythema; hence, the result may be considered negative or the study equivocal and inconclusive for skin sensitisation potential.

The predictions from databases DEREK, CEASAR, QSAR and PREDSKIN indicates positive predictions for skin sensitisation potential. However, the CEASAR database applicability domain is mostly based on data from aldehydes, and the proposed read across substances as weight of evidence for classification are not fit for purpose because of the differences in the chemical structures. PREDSKIN also added uncertainty for the hole read across approach as the Bayesian Outcome shows negative prediction for human maximization and human repeated insult patch test (HRIPT and HMT).

The conclusion by RAC is therefore that **no classification for skin sensitisation is warranted based on inconclusive data**.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The DS proposed no classification for STOT RE based on absence of data.

The notifier waived the request for short-term oral studies based on the argument that (3*E*)-3-decen-2-one occurs naturally in the diet and is approved as a direct food additive. The substance is not reported to be associated with sub-chronic toxicity nor is it metabolised to innocuous components. Structurally similar compounds did not cause adverse effects in rats exposed for 90 days and the developmental data shows very low toxicity potential.

Comments received during consultation

Comments in agreement with the DS proposal were received from one Company-Manufacturer and from one MSCA.

Assessment and comparison with the classification criteria

No repeated dose toxicity studies (28 or 90 days) were conducted with (3*E*)-3-decen-2-one.

For the comparison with structurally similar compounds, the notifier referred to studies described in the Joint FAO/WHO Expert Committee on Food Additives document (JECFA, 2003). In the EFSA evaluation (EFSA, 2010), a number of other studies using chemicals within flavouring groups 5 are described, that were evaluated at the 51st and 59th JECFA meeting (see the CLH report). While the majority of these substances indicate a low oral toxicity, a few do seem to induce adverse effects. For example, for 2-heptanone a NOAEL of 20 mg/kg bw/d and methyl-5-heptan-3-one a NOAEL of 82 mg/kg bw/d were found. In the US EPA hazard characterisation of 2-heptanone (June, 2010) a maternal NOAEL of 250 mg/kg bw/d is indicated from an oral prenatal developmental toxicity study in rats.

In comparison, the developmental toxicity study provided for (3*E*)-3-decen-2-one indicates a low oral toxicity with a NOAEL of 300 mg/kg bw/d based on a slight reduction in bodyweight gain; however, the dosing period was short (gestation day (GD) 9 to 16). Considering the natural occurrence in the diet, the metabolic pathways, and the low toxicity in the developmental toxicity study, it has been agreed that repeated dose oral toxicity studies are not required.

Therefore, RAC supports the proposal from the DS that **no classification can be concluded based on absence of data**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The DS proposed no classification for germ cell mutagenicity based on results from the *in vitro* and *in vivo* experiments.

(3*E*)-3-decen-2-one did not cause gene mutation in bacterial strains tested. It is considered to be mutagenic in the *in vitro* mouse lymphoma thymidine kinase locus in the cell line L5178Y without metabolic activation. However, (3*E*)-3-decen-2-one is considered to be non-mutagenic with respect to clastogenicity and/or aneugenicity in the *in vivo* mammalian erythrocyte micronucleus test and non-genotoxic in the UDS assay and *in vivo* Comet assay in duodenum and liver.

On the basis of the results of these studies, the DS concluded that (3*E*)-3-decen-2-one is not genotoxic.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

A summary of the studies included in the CLH dossier are presented below.

***Table**: Summary of submitted in vitro studies*

Method, guideline.	Test substance	Relevant information about the study	Observations
OECD TG 471,	(3*E*)-3-decen-	Test system: TA98, TA100, TA102, TA1535, TA1537	Negative with and

Method, guideline.	Test substance	Relevant information about the study	Observations
Ames test	2-one purity 98 %	Test concentrations: 0.0316-5.0 µL/plate Positive controls: 4-NOPD, NaN_3, MMS (-S9); 2-AA (+S9)	without S9
OECD TG 476, gene mutation test, mouse lymphoma cells	(3*E*)-3-decen-2-one purity 98 %	Test system: mouse lymphoma cells L5178Y Test concentrations: Exp I: 0.05-0.37 mM (+S9), 0.005-0.16 mM (- S9) Exp II: 0.10-0.38 mM (+S9), 0.0001-0.04 mM (-S9) Positive controls: BaP (+S9), EMS and MMS (-S9)	Negative with S9 **Positive without S9**

***Table**: Summary of submitted in vivo studies*

Method, guideline	Test substance,	Relevant information about the study (as applicable)	Observations
OECD TG 474, micronucleus	(3*E*)-3-decen-2-one purity 98 %	Test animal: mouse, NMRI 5/sex/dose Single i.p. dose Dose levels: 1 MTD, 0.5 MTD, 0.2 MTD	Negative
OECD TG 486, UDS test	(3*E*)-3-decen-2-one purity 98.6 %	Rat, Wistar Han 4/sex/dose Dose levels: 1000 and 2000 mg/kg bw	Negative
OECD TG 489, *in vivo* Comet assay	(3*E*)-3-decen-2-one purity 99.5 %	Rat, Wister Han 6 males/dose Dose levels: 500, 1000 and 2000 mg/kg bw/d Two consecutive doses, 24 hours apart	Negative (duodenum and liver)

MTD: maximum tolerated dose

Summary of in vitro studies

An Ames test was carried according to OECD TG 471 in five strains. No precipitation of the test item was observed in any of the tested strains used in experiment I and II, with and without metabolic activation. No toxic effects were observed in experiment I.

Under the test conditions, (3*E*)-3-decen-2-one did not induce point mutations in *S. typhimurium*.

A mammalian gene mutation test was carried out in mouse lymphoma cells L5178Y. The study was carried out according to OECD TG 476. Selection of exposure concentrations was based on data from a pre-experiment.

In experiment I with metabolic activation, all mutant values found were within the historical control of the test laboratory, no dose-relationship was observed, and the mutation frequencies found in the treated groups did not show a biologically relevant increase compared to solvent controls. However, this should be verified in an independent repetition experiment. In experiment II with metabolic activation, some of the mutant values observed were within the historical control data of the test laboratory. Some of the mutant values (at doses of 0.27, 0.31 and 0.38 mM) clearly exceeded the range of historical control data. In two dose groups, (0.31 and 0.38 mM) the threshold value of 2 for the mutation factor was slightly exceeded and a slight dose-response relationship could be observed. However, since in experiment I no mutagenicity was evaluated up to a relative total growth of 12.22 %, these results are considered to be equivocal.

In experiment II without metabolic activation, all mutant values recorded up to the dose of 0.0014 mM were within the historical control data of the test facility. At doses from 0.028 mM, the data exceeded the historical control range. In addition, in these dose groups the threshold value of 2 for the mutation factor was exceeded and a dose-response relationship could be

observed. An increase in small colonies noted at a dose of 0.034 mM suggests clastogenicity since corresponding mutagenicity was observed in this dose group.

Summary of in vivo studies

A **mouse micronucleus test** was performed with (3*E*)-3-decen-2-one. The dose groups were as follows: 1 MTD (50 % solution/kg bw), 0.5 MTD (25 % solution/kg bw), 0.2 MTD (10 % solution/kg bw) at 10 mL/kg bw via single i.p. administration.

All animals treated with the highest dose group (1 MTD) showed toxic effects. The animals treated with 25 % solution/kg bw (0.5 MTD) showed slight toxic effects after the treatment with the test item. No abnormalities were detected in the animals treated with 10 % solution/kg bw (0.2 MTD). The relative polychromatic erythrocytes (PCE) values measured for negative control animals were within historical controls. For the 0.2 MTD dose group, male PCE values were within the range of the study controls, females were reduced compared to controls, but the reduction was not statistically significant. The 0.5 MTD and 1 MTD dose groups showed reduced and increased values compared to control in males and females, respectively; the differences were not statistically significant. The micronucleated PCE values obtained for the negative control were within historical control data. For the 0.2 and 0.5 MTD dose groups, the values were within the range of corresponding negative controls. For the 1 MTD dose group, the values were within negative control values 44 hours after dosing. By 68 hours after dosing, the male values were reduced compared to the control values while the female values were increased, but the difference was not statistically significant. No biologically relevant increase of micronuclei was found after treatment with the test item in any of the dose groups evaluated.

Genotoxicity testing was performed in rat, according to OECD TG 486, UDS-test. In experiment I, initially two groups of four male rats were dosed orally at a dose volume of 10 mL/kg bw with the test item at doses of 2000 and 1000 mg/kg bw and two groups of four male rats were dosed with distilled water and N-2-fluorenylacetamide (2AAF, 50 mg/kg bw) as vehicle and positive controls respectively. Perfusion of livers commenced approximately 16 hours after dosing. The viability counts obtained from the initial experiment were lower than expected, and therefore, at the request of the sponsor, an exact repeat of experiment I was performed.

Experiment II was performed in exactly the same way as experiment I except that the positive control was N,N'-dimethylhydrazine dihydrochloride (NDHC) and liver perfusion started approximately 4 hours after dosing.

There were no premature deaths or any clinical signs in any of the dose groups. For some animals in experiment I, the cell viability was substantially less than 50 %, which was considered to be due to high collagenase potency, and though the cells were processed and scored, the experiment was repeated. In both experiments, cell viability was considered acceptable. The test item did not induce any marked increases in the incidence of cells in repair at either dose level as no significant increase compared to control was observed in the treatment groups. In the two experiments, the net nuclear gain counts (N-C) were outside the typical range of -2 to -6 in the vehicle and test item dose groups; however, these values were considered to be due to experimental variation and therefore acceptable. The positive controls induced a marked increase in the percentage of cells in repair, thus demonstrating the viability of the test. Under the test conditions the substance was considered to be non-genotoxic.

An *in vivo* Comet assay was carried out in which (3*E*)-3-decen-2-one was administered to groups of 6 male Wistar rats in two consecutive doses 24 hours apart at dose levels of 500, 1000 and 2000 mg/kg bw/d. The mean and median % tail intensity (% TI) from (3*E*)-3-decen-2-one treated animals compared with vehicle control values were used to assess the DNA strand breaks. No statistically significant increases in the median % TI were observed in either the duodenum or liver of male Wistar rats at any dose level, compared to vehicle control values. The positive

control compound, ethyl methane sulphonate, produced statistically significant increases in the median % TI in the duodenum and liver ($p < 0.001$) when compared to vehicle control values. Consequently, (3*E*)-3-decen-2-one did not demonstrate any evidence of causing an increase in DNA strand breaks or cytotoxicity in either the duodenum or liver of male Wistar rats when administered orally.

Conclusion by RAC

(3*E*)-3-decen-2-one did not cause gene mutation in bacterial strains tested. The substance was considered to be mutagenic in the *in vitro* mouse lymphoma thymidine kinase locus in the cell line L5178Y without metabolic activation.

However, (3*E*)-3-decen-2-one was considered to be non-mutagenic with respect to clastogenicity and/or aneugenicity in the *in vivo* mammalian micronucleus test and non-genotoxic in the UDS assay and *in vivo* Comet assay in duodenum and liver.

On the basis of the results of these studies, and in line with the DS proposal, RAC concludes that **no classification is warranted for (3*E*)-3-decen-2-one**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

No data were included in the CLH report.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC concludes that **no classification can be concluded based on absence of data**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The DS proposed no classification for adverse effects on sexual function and fertility, due to the lack of data: no reproductive toxicity study is available, and no investigation of reproductive organs was conducted in the repeated dose inhalation study.

No classification on developmental toxicity was proposed by the DS based on results from a developmental study in rats where the NOAEL was found to be 1000 mg/kg bw/d.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

RAC concludes that **no classification can be concluded for adverse effects on sexual function and fertility based on absence of data**.

Adverse effects on development

The summary of the study on developmental toxicity included in the CLH dossier on developmental toxicity.

***Table**: Summary of submitted developmental toxicity study*

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**
OECD TG 414, prenatal developmental toxicity study Rat, Sprague-Dawley, 24 females	(3*E*)-3-decen-2-one (batch AMV-1018), purity 99.81 % 0, 100, 300, 1000 mg/kg bw/d GD6-19	NOAEL maternal: 300 mg/kg bw/d based on slightly reduced bodyweight gain (-12 %) NOAEL developmental: 1000 mg/kg bw/d

In this developmental study, groups of 24 female Sprague-Dawley were treated with (3*E*)-3-decen-2-one at gavage doses of 0, 100, 300 and 1000 mg/kg bw/d during GD6 to 19 according to OECD TG 414.

No mortalities or clinical signs of toxicity were observed. The only significant effect was a slight decrease in food consumption and corrected body weight gain at the high dose. No effects on macropathology, pregnancy outcome, foetal body weight or foetal development were observed. The developmental NOAEL was set at 1000 mg/kg bw/d and the maternal NOAEL at 300 mg/kg bw/d based on the reduction in body weight gain.

Conclusion by RAC

Developmental toxicity was assessed with a prenatal developmental toxicity study according to OECD TG 414. In this study, neither mortality nor clinical signs of toxicity and no effects on macropathology, pregnancy outcome, foetal body weight or foetal development were observed. The only significant effect was a reduced corrected body weight gain (-5.7 %) at the high dose (1000 mg/kg bw/d). Consequently, RAC agrees with the DS that a **classification for adverse effects on development is not warranted**.

Effects on or via lactation

No data are available to assess this hazard class, therefore RAC concludes that **no classification can be concluded based on absence of data**.

RAC evaluation of aspiration toxicity

Summary of the Dossier Submitter's proposal

The DS proposed classification as Asp. Tox. 1 based on results from measured kinematic viscosity. The measured kinematic viscosity is 2.21 mm^2/s (25 °C) and 1.76 mm^2/s (45 °C). The criterion for classification is 20.5 mm^2/s or below.

Comments received during consultation

One Company-Manufacturer disagreed with the decision, indicating that (3*E*)-3-decen-2-one actually does not meet criterion 1 (no reliable and good quality human evidence is available) and only partially criterion 2 (kinematic viscosity). However, the substance is not a pure hydrocarbon. The substance should therefore not be classified.

Assessment and comparison with the classification criteria

The following measurements are noted in the CLH report.

Table: *Summary of the submitted data on aspirational hazard*

Property	Value	Reference	Comment (e.g., measured or estimated)
Kinematic viscosity	2.21 mm^2/s (25 °C) 1.76 mm^2/s (45 °C)	Bradbury (2010)[a]	Measured
Dynamic viscosity	1.858 mPa.s (25 °C) 1.475 mPa.s (45 °C)	Bradbury (2010)[a]	Measured

[a] As summarised in the DAR (Volume 3, annex B.2)

No information is available regarding aspiration in humans (cases).

The kinematic viscosity of (3*E*)-3-decen-2-one at 40°C is between 1.76 and 2.21 mm^2/s. The substance contains mainly carbon and hydrogen atoms but also one oxygen atom. Based on the skin irritating and lung irritating/corrosive properties after dermal and inhalation exposure, it can be expected that also aspiration of liquid (3*E*)-3-decen-2-one will cause lung irritation or corrosivity.

Classification is required when there is reliable and good quality human data or when the substance is a hydrocarbon with a kinematic viscosity of 20.5 mm^2/s or less.

The first criterion is not fulfilled as no human cases of aspiration are known. The second criterion is only partially fulfilled as the kinematic viscosity of (3*E*)-3-decen-2-one is below the cut-off but, (3*E*)-3-decen-2-one is not a hydrocarbon in the strict sense as it also contains one oxygen atom. However, seeing the irritating or corrosive properties to the lung after inhalation exposure of (3*E*)-3-decen-2-one, it is considered likely that aspiration of the liquid will also result in lung irritation or corrosion.

Therefore, RAC agrees with the DS that **classification as Asp. Tox. 1 is warranted**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

There is no current entry in Annex VI of the CLP Regulation for the substance (3*E*)-dec-3-en-2-one.

The DS proposed to classify the substance as Aquatic Chronic 2; H411, the substance being not rapidly degradable, based on the **surrogate approach** and the lowest EC_{50} obtained with

Oncorhynchus mykiss (1.50 mg/L, mean measured (mm)) due to no chronic aquatic toxicity data available for the most acutely sensitive species (fish).

The physico-chemical characteristics show that (3*E*)-dec-3-en-2-one has moderate water solubility (140 mg/L at 24 °C), vapour pressure of 430 Pa at 25 °C and the Henry's law constant was estimated to be 473.8 $Pa \times m^3 \times mol^{-1}$, indicating high volatility.

Degradation

A summary of the relevant information on degradation is provided in Table 34 of the CLH report.

Abiotic degradation

A preliminary OECD TG 111 study has been presented (Benton, 2011). The hydrolytic stability of (3*E*)-dec-3-en-2-one was studied in sterile aqueous buffer solutions at pH 4, 7 and 9 showing that the substance was unstable, with losses of 34, 41 and 63 % at a pH of 4, 7 and 9 respectively. No DT_{50} values were presented. Additional testing was not considered to give relevant scientific information due to quick dissipation from water by volatilisation (Henry's law constant = 473.8 $Pa \times m^3 \times mol^{-1}$).

A scientific justification was additionally provided based on literature information supporting that the substance molecule would not be reactive to hydrolysis under the normal conditions employed within the OECD study guideline thus (3*E*)-dec-3-en-2-one is considered hydrolytically stable. (3*E*)-3-decen-2-one is manifested by the fragmentation of the alkene bond and that reaction only occurs at elevated temperatures and elevated pressures and even that reaction is not highly efficient (Freedlander, 2014).

No studies were submitted for photodegradation in water due to (3*E*)-dec-3-en-2-one not showing absorption above 270 nm and not showing a significant route of degradation/dissipation in the aquatic environment.

Model US EPA AOP v1.92 and Atkinson method were used to calculate the indirect photo-oxidation assuming an atmospheric hydroxyl radical concentration of 1.5×10^6 cm^{-3} and resulting in a DT50 of 2h for both the cis and trans isomers indicating (3*E*)-dec-3-en-2-one would not be subject to long range atmospheric transport (Benton, 2011).

Biodegradation

Ready biodegradation

A valid OECD TG 301F manometric respirometry test has been presented that was conducted under aerobic conditions in activated sludge and run at the loading of 105 mg/L of (3*E*)-dec-3-en-2-one corresponding to an oxygen demand of about 305 mg/L (T_hODNH_4). The preparation of the test solutions included (3*E*)-dec-3-en-2-one (duplicate), inoculum control (duplicate), procedure (single), abiotic (single) and toxicity controls (single). The T_hODNH_4 of (3*E*)-dec-3-en-2-one was calculated to be 2.904 mg O_2/mg test item.

The degradation was more than 60 % after 4 days of incubation. The difference between duplicate values of degradation at the end of the test was less than 20 %. In the toxicity control 34 % biodegradation was noted within 14 days and 46 % after 28 days. The test item was assumed to be not inhibitory to aerobic activated sludge due to degradation > 25 % within 14 days.

The mean percentage biodegradation for (3*E*)-dec-3-en-2-one at the end of the 28-day exposure was 60 % (T_hODNH_4); duplicate 1 = 60 % and duplicate 2 = 59 %. 10 % of biodegradation was already reached at day 3 (duplicate 1 = 12 %; duplicate 2 = 17 %), but the pass level of 60 % was only reached at day 28, therefore it was concluded that the 10-day window was not met. (3*E*)-dec-3-en-2-one was tested in all studies, including ready biodegradability, and contains the

cis (Z) isomer as minor component (% not specified). No information was given on the potential differences in biodegradability of the cis/trans isomers.

There are no simulation data available for the water, water-sediment or soil compartments.

Overall, the DS considered the available data adequate for classification purposes and concluded that (3*E*)-dec-3-en-2-one is considered not rapidly degradable in the aquatic environment, according to the CLP criteria.

Bioaccumulation

A summary of the available information on bioaccumulation is provided in Table 35 of the CLH report.

There are two studies available that experimentally determined the $logK_{ow}$ of (3*E*)-dec-3-en-2-one using the shake-flask methodology (OECD TG 107). Wo (2009) reported a $logK_{ow}$ of 3.45 ± 0.02 at pH 5.8 and 24 °C, while Benton (2011) reported $logK_{ow}$ values of 3.45, 3.47 and 3.43 at pH 4, 7 and 9 at 22 °C, respectively. As the surface tension of (3*E*)-dec-3-en-2-one is < 60 mN/m (~30 mN/m) which is considered surface active the experimentally determined values should be considered with care. Based on the solubility in water (0.14 g/L) and in n-octanol (expected > 250 g/L), the $logK_{ow}$ can be estimated to be ~3.25. Estimated values using BioLoom v1.5 and Kowwin v1.68, are 3.16 and 3.28, respectively. The DS considered the experimental $logK_{ow}$ value of 3.45 acceptable.

No experimental studies on bioaccumulation in fish are available.

Using the experimentally determined $logK_{ow}$ of 3.45, a BCF of 171 L/kg was estimated using the following relation as defined by Veith *et al.* 1979 (based on chemical class: pesticides): $logBCF = 0.85\ logK_{ow} - 0.70$. Two other QSARs were also used to calculate the BCF, i.e. $logBCF = 0.76\ logK_{ow} - 0.23$ (Veith *et al.* 1979, based on chemical class: various organic chemicals) producing a BCF of 247 L/kg and $logBCF = logK_{ow} - 1.32$ (Mackay, 1982) producing a BCF of 135 L/kg. Additionally, BCF values were calculated using the BCFBAF (v3.01) module provided in the EPI Suite™. BCFBAF estimates fish bioconcentration factor and its logarithm using two different methods. By default, BCFBAF uses the $logK_{ow}$ calculated by the KOWWIN module. However, the assessor used for this proposal the higher experimentally determined value of 3.45 instead of the KOWWIN estimated value of 3.28, which resulted in slightly higher BCF values of 87.8 L/kg wwt (regression-based method) and 138 L/kg wwt (Arnot-Gobas (upper trophic) method).

Three QSAR estimates are also presented: USES Koc (L/kg) = 785 L/kg, based on $logK_{ow} = 3.45$ and depending on the QSAR model, the proposed Koc for (3*E*)-dec-3-en-2-one varies between 165.2 L/kg and 1069 L/kg using EpiSuite™ (KocWin) and EpiSuite™ (KocWin respectively.

Overall, as the experimentally determined and the estimated $logK_{ow}$ values are below the threshold of $logK_{ow} \geq 4$, and due to the QSAR estimated values being below the trigger value of 500 L/kg, the DS considered **(3*E*)-dec-3-en-2-one to have low bioaccumulation potential**.

Aquatic toxicity

Aquatic acute toxicity

A summary of the relevant information on aquatic acute toxicity is presented in Table 36 of the CLH report.

The DS noted that the aquatic toxicity studies were performed with (3*E*)-dec-3-en-2-one, lot HA-2010/01 (purity 98.6 %) and AMV-1018 (purity 99.4 %) which primarily consisted of the substance itself (3*E*)-dec-3-en-2-one (trans-isomer) and contained minor amounts of the cis-isomer. There is no information available regarding differences in toxicity between isomers.

Aquatic acute toxicity studies are presented for all three trophic levels: fish, invertebrates, and algae and aquatic plants.

One valid OECD TG 203 acute fish toxicity study is available with *Oncorhynchus mykiss* in a semi-static test design. No accurate mean measured concentrations could be calculated for nominal test concentrations of 0.13 and 0.28 mg/L. Test endpoints were based on geometric mean measured concentrations of the two highest test concentrations presenting an LC_{50} of 1.50 mg/L (mm) after 96 h of exposure. (Anonymous, 2011a)

For invertebrates, one reliable acute study has been given. The *Daphnia magna* OECD TG 202 immobilisation test provided an LC_{50} of 1.68 mg/L (mm) after 48h exposure. No accurate mean measured concentrations could be calculated for nominal test concentrations of 0.19 and 0.43 mg/L, as these nominal concentrations were below the LOQ of the analytical method. This is acceptable since these two concentrations are not relevant for estimation of the EC_{50} value (Hoffman and Deierling, 2011b).

One reliable OECD TG 201 study is available with *Pseudokirchneriella subcapitata* showing a 72 h E_rC_{50} value of 2.8 mg/L (mm). A measured concentration of 0.095 mg/L was obtained (15 % of the 0-Hour measured concentration) indicating that the test item was unstable due to chemical adsorption to the algal cells thus geometric mean measured concentrations were calculated (Vryenhoef, 2016).

Another supportive OECD TG 221 study is available with *Lemna gibba* showing E_rC_{50} of 2.84 mg/L (mm) based on frond number (Hoffman and Deierling, 2012).

According to the provided valid studies, fish are found to be the most sensitive species. The lowest EC_{50} is obtained with *O. mykiss* (1.50 mg/L (mm)) not meeting the CLP classification criteria for aquatic acute hazards so the **DS proposed not to classify (3*E*)-dec-3-en-2-one for acute aquatic hazards, based on the L(E)C_{50} ≥ 1 mg/L in CLP Table 4.1.0 (a).**

Aquatic chronic toxicity

A summary of the relevant information on aquatic acute toxicity is presented in Table 46 of the CLH report.

Valid data for aquatic chronic toxicity is only presented for one trophic level: algae and aquatic plants. No long-term fish and invertebrate tests are available.

The OECD TG 201 study with *P. subcapitata* resulted in a NOE_rC of 0.34 mg/L (mm) and E_rC_{10} of 0.63 mg/L (mm) (Vryenhoef, 2016).

The OECD TG 221 growth inhibition test (static, 7 d) with *L. gibba* resulted in a NOEC of 0.29 mg/L (mm) and E_rC_{10} of 1.03 mg/L (mm) based on based on frond number (Hoffman and Deierling, 2012).

Since no chronic aquatic toxicity data were available for fish and invertebrates but fish species are acutely the most sensitive endpoint, the DS considered based on a surrogate approach and for a not rapidly degradable substance that **(3*E*)-dec-3-en-2-one fulfils the criteria for classification as Aquatic Chronic Category 2; H411 based on the L(E)C_{50} > 1 and ≤ 10 mg/L in CLP Table 4.1.0 (b)(iii).**

Comments received during consultation

One Company-Manufacturer indicated that the proposed classification proposal as Aquatic Chronic 2 is not warranted based on the substance not persisting, in their opinion, in the aquatic environment due to a combination of degradation and very significant volatilisation. A 28-day

study on the emergence of *chironomids* demonstrating low toxicity (NOEC = 103 mg/kg sediment/d; AMVAC ref. no. 965-AQU-007) is also mentioned.

With regard to the biodegradability, the DS responded by referring to the CLP Regulation and cases where the 10-day window can be waived. It was indicated that none of these conditions was met and the 10-day window requirement should be fulfilled so that the substance be considered not rapidly degradable. The DS also noted that the study with *Chironomus riparius* was not available until after the CLH report was submitted to the ECHA and has not been evaluated. Despite the fact that a chronic study for fish is not available, the "most stringent" classification would anyway be used warranting the same proposal for classification as Aquatic Chronic 2.

One MSCA agreed with the classification proposal as Aquatic Chronic 2; H411. Further information was requested on the identity and the CAS number of the substance as the CLH dossier and the available DAR refers to different CAS numbers for the same substance.

The DS explained that CAS 18402-84-1 specifically relates to the '3-Entgegen'-isomer (3*E*) 3-decen-2-one that is the active substance and should be preferred, whereas CAS 10519-33-2 refers to '3-decen-2-one', i.e., no stereoisomer in specific, which is inaccurate.

Assessment and comparison with the classification criteria

The CLH report did not include information on the photodegradation in water and behaviour in the water-sediment system.

RAC agrees with the DS to consider volatilisation as the primary route of dissipation based on the Henry's law constant and that the hydrolysis is limited route of degradation for (3*E*)-dec-3-en-2-one in the aquatic environment. Furthermore, the substance can be considered indirectly photodegradable.

According to the available data presented by the DS, the test material (purity 98.6 %) containing both the trans-isomer (3*E*)-dec-3-en-2-one and the cis (Z) isomer was found to be 60 % biodegraded to CO_2 over a test period of 28 days. The cis (Z) isomer was only present as a minor component (exact amount is not specified). Both isomers are expected to show similar biodegradation behaviour but no information is given on the potential differences in biodegradability of the cis/trans isomers.

RAC notes that during the test, the degradation of (3*E*)-dec-3-en-2-one did not meet the 10-day window, thus the substance is not demonstrated to be readily biodegradable in a 28-day test for ready biodegradability as the pass level of the test must be achieved within 10 days from the onset of biodegradation, according to Section 4.1.2.9.5 of the CLP regulation.

The 10-day window condition may be waived as discussed in the CLP regulation Annex II.2.3. If this is not possible, then the pass level should be evaluated within a 14-day window if possible, or after the end of the test. RAC concludes that there is currently not sufficient justification that the 10-day window condition may be waived.

Based on the available data on the hydrolytic behaviour of the substance in the water demonstrating stability, the additional justifications on the unreactive nature of the structure of the substance and due to the degradation of (3*E*)-dec-3-en-2-one amounting to 60 % after 28 days based on oxygen consumption, equalling the pass level of 60 % (theoretical oxygen demand), RAC agrees with the DS to consider (3*E*)-dec-3-en-2-one as **not rapidly degradable** for classification purposes.

There are no experimental bioaccumulation studies available for fish species. However, the available data on the experimentally determined $\log K_{ow}$ and the estimated BCF values can be

considered sufficient to come to conclusion on the bioaccumulation potential of the substance. RAC agrees with the DS and concludes that (3*E*)-dec-3-en-2-one has **low potential for bioaccumulation** based on the experimentally determined the $logK_{ow}$ 3.45 ± 0.02 at 24 °C which is below the threshold of $logK_{ow} \geq 4$ and the QSAR estimated BCF values in the range 87.8-247 L/kg wwt well below the cut-off value of 500 L/kg.

RAC notes that no data has been provided as part of the CLH dossier showing toxicity of the degradation products so they are not taken into account for classification purposes. RAC also notes that the study with *Chironomus riparius* mentioned during the consultation round has not been evaluated and taken into account as part of this proposal.

RAC agrees with the DS that, based on the most sensitive fish species result (LC_{50} of 1.50 mg/L for *O. mykiss*), together with the other scientifically robust and reliable acute data, **no classification for aquatic acute hazards** is warranted.

Taking into account that reliable chronic data is not available for all trophic levels, RAC agrees with the DS proposal RAC to classify the substance as **Aquatic Chronic 2; H411,** with the substance being not rapidly degradable and based on the application of CLP Table 4.1.0 (b)(i) and (b)(iii) that both lead to Aquatic Chronic 2.

RAC notes that if additional data become available either on the biodegradation, bioaccumulation potential and the degradation products in the environment and acute or chronic toxicity of (3*E*)-dec-3-en-2-one and its metabolites or isomers, the classification could be reconsidered.

Additional references

Buehler. Occlusive patch method for skin sensitization in guinea pigs: the Buehler method. Food Chem Toxicol. 1994 Feb;32(2):97-101

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).