KEMI
Swedish Chemicals Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Citronellal

EC No 203-376-6

CAS No 106-23-0

Evaluating Member State: Sweden

Dated: 29 April 2016

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2015

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Citronellal was originally selected for substance evaluation in order to clarify concerns about:

- human health/sensitiser

- exposure/wide dispersive use, consumer use, exposure of workers, high (aggregated tonnage)

The evaluation was limited to clarifying initial grounds for concern.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

On 18 September 2013, the Registrant of citronellal was addressed a compliance check (CCH) decision by ECHA[2] (decision number: CCH-D-0000002945-66-03/F).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State (eMSCA) to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	✓
No need for regulatory follow-up action at EU level	

[2] Available on the ECHA website, http://echa.europa.eu/information-on-chemicals/dossier-evaluation-decisions.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

The eMSCA revised the Derived No Effect Level (DNEL) for skin sensitisation for citronellal by applying an additional assessment factor of 3-fold for possible matrix/vehicle effect.

The Risk Characterisation Ratios (RCRs) (with the revised eMSCA DNEL for skin sensitisation) for dermal long-term local effects to workers for the uses of citronellal given in the table below are above 1.

Table 2

Population	Exposure Scenario	RCRs (with $DNEL_{eMSCA}$) for dermal long-term local route
Industrial workers	Manufacturing – 'contributing scenarios (3), (4), and (9) for PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises or PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities'.	>2
Professional workers	Formulation use – 'contributing scenario (4) for PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)'	>1

The highest concentration of citronellal reported by the Registrant in the exposure scenarios for the use in cleaning agents by professional workers is <1%. The eMSCA finds from the Swedish Product Register that there are such products on the Swedish market used by workers with much higher concentration of citronellal leading to RCR (with the revised eMSCA DNEL for skin sensitisation) well above 1 for dermal long-term local route.

Table 3

Population	Use of products with highest concentration on the Swedish market	RCRs (with $DNEL_{eMSCA}$) for dermal long-term local route
Professional workers	Use in cleaning agents – Professional	>5

The eMSCA recommends the Registrant of citronellal to use the DNEL for skin sensitisation as revised by the eMSCA and consequently, revise the Chemical Safety Assessment.

The eMSCA will inform the National Enforcement Authorities (NEAs) via PD NEA (Portal Dashboard NEA) or Forum (the Forum for Exchange of Information on Enforcement) about possible much higher concentrations of citronellal in products in the EU market for professional workers, than that indicated in the exposure scenarios by the Registrant. The NEAs may further consider to inspect if the Downstream Users are using citronellal safely.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Table 4

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Information to the National Enforcement Authorities	August 2016	Sweden

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Citronellal was originally selected for substance evaluation in order to clarify concerns about:

- human health/sensitiser

- exposure/wide dispersive use, consumer use, exposure of workers, high (aggregated tonnage)

The evaluation was limited to clarifying initial grounds for concern.

Table 5

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
DNEL for skin sensitisation	The eMSCA recommends to revise the DNEL for skin sensitisation by applying an assessment factor of at least 3-fold for possible matrix/vehicle effect.
Risks for skin sensitisation to workers and consumers	With eMSCA's revised DNEL for skin sensitisation, there are risks of dermal long-term local effects to workers.

7.2. Procedure

The updated Community rolling action plan (CoRAP) was published on the ECHA website on 17 March 2015.

The current evaluation is based on the dossier update submitted by the Registrant on 10 September 2014.

Since the evaluation is limited to clarifying the initial grounds for concern that relate to skin sensitisation and the exposure of humans, other health hazards, physical hazards or environmental hazards and environmental exposure assessment were not evaluated.

The evaluating Member State Competent Authority (eMSCA) is of the opinion that the information available in the registration dossier and other relevant and available information is enough to clarify the concern and thus no draft decision was prepared.

7.3. Identity of the substance

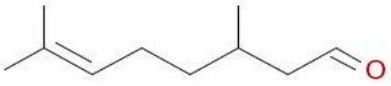
Table 6

SUBSTANCE IDENTITY	
Public name:	citronellal
EC number:	203-376-6

CAS number:	106-23-0
Index number in Annex VI of the CLP Regulation:	NA
Molecular formula:	$C_{10}H_{18}O$
Molecular weight range:	154.249
Synonyms:	6-Octenal, 3,7-dimethyl- 3,7-dimethyloct-6-enal

Type of substance: Mono-constituent

Structural formula:



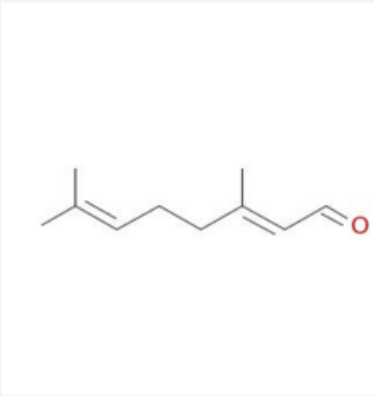
Identity of read-across substance

Table 7

IDENTITY OF READ-ACROSS SUBSTANCE	
Public name:	Citral
EC number:	226-394-6
CAS number:	5392-40-5
Index number in Annex VI of the CLP Regulation:	605-019-00-3
Molecular formula:	$C_{10}H_{16}O$
Molecular weight range:	152.233
Synonyms:	Reaction mass of (E)-3,7-dimethylocta-2,6-dienal and (Z)-3,7-dimethylocta-2,6-dienal 2,6-Octadienal, 3,7-dimethyl-
Type of substance:	Multi-constituent

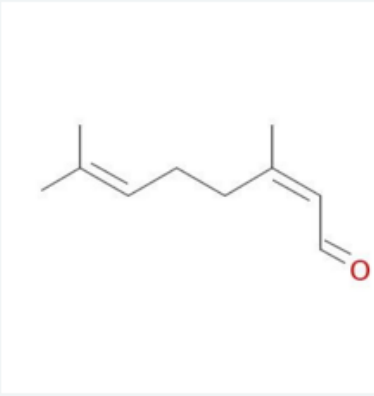
Structural formula of read-across substance:

Constituent 1



Reference substance name:	(E)-3,7-dimethylocta-2,6-dienal
EC Number:	205-476-5
EC Name:	(E)-3,7-dimethylocta-2,6-dienal
CAS Number:	141-27-5
Molecular formula:	C10H16O
IUPAC Name:	(E)-3,7-dimethylocta-2,6-dienal

Constituent 2



Reference substance name:	(Z)-3,7-dimethylocta-2,6-dienal
EC Number:	203-379-2
EC Name:	(Z)-3,7-dimethylocta-2,6-dienal
CAS Number:	106-26-3
Molecular formula:	C10H16O
IUPAC Name:	(Z)-3,7-dimethylocta-2,6-dienal

7.4. Physico-chemical properties

Table 8

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	liquid
Boiling point	206.9 °C at 1013 hPa
Vapour pressure	0.26 hPa at 25 °C
Water solubility	88 mg/L and 25 °C
Partition coefficient n-octanol/water (Log Kow)	3.62 at 25 °C

7.5. Manufacture and uses

7.5.1. Quantities

Table 9

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☒ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t

☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 10. Overview of uses from ECHA dissemination webpage

USES Use(s)	
Uses as intermediate	-
Formulation	Formulation of preparations
Uses at industrial sites	Intermediate use
Uses by professional workers	In cleaning agents
Consumer Uses	In cleaning agents, air care products, cosmetics, fragrances and biocidal products
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

None

7.6.2. Self-classification

- In the registration:

Skin Irrit. 2 H315: Causes skin irritation
Eye Irrit. 2 H319: Causes serious eye irritation
Skin Sens. 1B H317: May cause an allergic skin reaction

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

Skin Sens. 1 H317: May cause an allergic skin reaction
Aquatic Chronic 2 H411: Toxic to aquatic life with long lasting effects
STOT SE 3 H335: May cause respiratory irritation

7.7. Environmental fate properties

Not relevant for this evaluation.

7.8. Environmental hazard assessment

Not relevant for this evaluation.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Information on the toxicokinetics of citronellal from the experimental studies is limited to details on metabolites. These studies include three *in vivo* and two *in vitro*, all with a reliability score 2 (reliable with restrictions), reported in a weight of evidence type in the registration dossier. The Registrant performed a read-across to the structural analogue citral (EC No 226-394-6) comparing the structure, molecular weights, lipophilicity, water solubility and volatility. An *in vivo* experimental study (with reliability score 2) on the disposition of citral is reported as the key study in the registration dossier.

Based on the log K_{ow} value of citronellal (3.62) and dermal absorption data on citral (50% dermal penetration rate set based on three *in vivo* and one *in vitro* studies), the Registrant assumed a dermal penetration rate of 50% for citronellal for derivation of dermal DNELs. The eMSCA can support the use of this value.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated. The Registrant has self-classified citronellal as Skin Irrit. 2, H315: Causes skin irritation.

7.9.3. Sensitisation

The Registrant has self-classified citronellal as Skin Sens. 1B, H317: May cause an allergic skin reaction.

One Local Lymph Node Assay (LLNA) on citronellal, which is the only study with reliability score 1 (reliable without restriction), is reported in the registration dossier. In this study the EC3 value was found to be above 30% (7500 µg/cm^2). Five studies in guinea pigs with citronellal are reported in the registration dossier with a reliability score 2 (reliable with restrictions). In one of those guinea pigs studies citronellal at 0.1% induction dose did not show positive reactions in any animals but among the remaining studies citronellal at 3% induction dose showed positive reactions in upto 100% of animals. Further, following studies in humans with reliability score 2 are reported in the registration dossier: one Human Repeated Insult Patch Test (HRIPT), one Human Maximisation Test (HMT), and three diagnostic patch tests. In the HRIPT study none of 104 subjects had positive reaction to 10% citronellal in petrolatum whereas 10 of 73 subjects were tested positive to 10% citronellal in ethanol. The lowest observed adverse effect level (LOAEL) in this study was estimated as approx. 5000 µg/cm^2. In the HMT study none of 25 subjects had positive reaction to 4% citronellal in petrolatum. The No observed Effect Level (NOEL) in this study was calculated as 3000 µg/cm^2.

For citral, the structural analogue of citronellal, Lalko and Api (2008) reviewed several studies including eleven LLNAs, sixteen studies in guinea pigs, five HRIPTs, fourteen HMTs, and eleven human diagnostic patch tests in order to identify a threshold for induction of skin sensitisation to citral. The weighted mean of EC3 values from eleven LLNAs is 5.7% (1414 µg/cm^2) depending on the vehicle used (ethanol:diethyl phthalate or acetone:olive oil (4:1)). In this comprehensive review it was concluded "by a weight of evidence that the human NOEL for induction of sensitization to citral is 1400 µg/cm^2."

The Registrant of citronellal, as a conservative approach, selects a NOEL of 1400 µg/cm^2 for induction of skin sensitisation to citronellal.

7.9.4. Repeated dose toxicity

Not evaluated.

7.9.5. Mutagenicity

Not relevant for this evaluation.

7.9.6. Carcinogenicity

Not relevant for this evaluation.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Not relevant for this evaluation.

7.9.8. Hazard assessment of physico-chemical properties

Not relevant for this evaluation.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The Registrant identified skin sensitisation as the most sensitive endpoint to set DNEL for dermal long-term local effects and the NOEL of 1400 µg/cm^2 is used as a starting dose descriptor value to derive DNEL for skin sensitisation. The eMSCA used the same starting dose descriptor value to revise the DNEL for skin sensitisation.

The Registrant applied only an assessment factor (AF) of 10 for intraspecies differences when deriving skin sensitisation DNEL for workers and general population. Since the NOEL is derived from human data, no interspecies AF is applied. Therefore, the Registrant's DNEL for induction of skin sensitisation to citronellal is

$DNEL_{Registrant}$ = NOEL/overall AF = 1400 µg/cm^2/10 = 140 µg/cm^2

Appendix R. 8-10 to the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health (version 2.1, November 2012), provides additional guidance on setting a DNEL for skin sensitisation for cases where reliable dose descriptors are available.

Citronellal is used in different products which might contain different matrices than the one used in the experimental test systems. If a product contains substances with irritant or/and penetration enhancing properties it might increase the potential of citronellal for induction of sensitisation. According to Appendix R. 8-10, the application of an additional AF of 1-10-fold should be considered depending on the information available on the vehicle or matrix relevant for human exposure. An AF of 3 has to be applied if human exposure is expected in a matrix even with no penetration enhancers or irritants. Furthermore, an additional AF of 1-10-fold should be considered to account for specific exposure conditions concerning situations when the experimental set up (animal or human) differs from actual human exposure conditions, by e.g. different parts of the body being exposed, differences in skin integrity caused by specific human activities, occlusion of the exposed skin and differences in exposure frequency between the animal/human study and actual human exposure situation.

The eMSCA recommends to revise the DNEL for skin sensitisation by applying at least an additional AF of 3-fold for possible matrix/vehicle effect as explained above while acknowledging this being a less conservative approach. The overall AF would then be 30 (10 (intraspecies AF) * 3 (matrix/vehicle effect AF)). Therefore, the eMSCA's proposed DNEL for induction of skin sensitisation to citronellal is

$DNEL_{eMSCA}$ = NOEL/overall AF = 1400 µg/cm^2/30 = 47 µg/cm^2

It is to be noted that in the proposed DNEL by eMSCA no AFs were applied to account for specific exposure conditions as discussed above. The eMSCA recommends the Registrant and/or the Downstream Users of citronellal to take this uncertainty into account while performing the chemical safety assessment.

Table 11

CRITICAL DNEL FOR WORKERS AND GENERAL POPULATION						
Endpoint of concern	**Type of effect**	**Critical study**	**Corrected dose descriptor**	**DNEL**		**Justification/ Remarks**
				Registrant	**eMSCA**	
Skin sensitisation	Long-term dermal – local effects	Lalko and Api, 2008 (on the structural analogue citral)	NOEL: 1400 µg/cm²	140 µg/cm²	47 µg/cm²	eMSCA applied an additional AF of 3-fold for possible matrix/vehicle effect to derive the DNEL for this endpoint.

Important note: "In case of skin sensitisation, the first step should always be a qualitative approach to assessing and controlling the risks and setting a DNEL (if possible) could be used to judge the remaining/residual likelihood of risks" (ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health (version 2.1, November 2012)).

7.10. Assessment of endocrine disrupting (ED) properties

Not relevant for this evaluation.

7.11. PBT and VPVB assessment

Not relevant for this evaluation.

7.12. Exposure assessment

7.12.1. Human health

The Registrant generated exposure scenarios and made exposure estimations for manufacture and for all the identified uses of citronellal (viz., see below) using EasyTRA 4.0 model[3].

1. Manufacturing of the substance
2. Compounding
3. Formulation
4. Intermediate use
5. Use in cleaning agents – Professional
6. Use in air care
7. Use in cosmetics
8. Use in cleaning agents – Consumers
9. Other consumer use as fragrance material

[3] www.easytra.com, last accessed 16 March 2016.

In the eMSCA's opinion the Registrant has adequately described the operational conditions and the risk management measures for all the scenarios.

7.12.1.1. Worker

In the registration dossier the highest exposure value estimated for workers for dermal long-term local route is between 75 and 100 µg/cm^2 for the manufacturing – 'contributing scenarios (3), (4), and (9) for PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises or PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities'.

The second highest exposure value estimated for workers for dermal long-term local route is between 47 and 50 µg/cm^2 for the formulation use – 'contributing scenario (4) for PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)'.

The highest concentration of citronellal reported by the Registrant in the exposure scenarios for the use in cleaning agents by workers (professional) is <1%. The eMSCA finds from the Swedish Product Register that there are such products on the Swedish market used by workers with concentration of citronellal much higher than 1%.

7.12.1.2. Consumer

In the registration dossier exposure values of <47 µg/cm^2 are estimated for dermal long-term local route for all the consumer uses identified.

7.12.2. Environment

Not relevant for this evaluation.

7.12.3. Combined exposure assessment

As skin sensitisation is considered to be mainly a threshold concentration effect, it may be less relevant to perform a combined exposure assessment and therefore this has not been done.

7.13. Risk characterisation

With eMSCA's revised DNEL for skin sensitisation, the RCRs for dermal long-term local route for all consumer users are below 1. However, for workers (industrial and professional) the RCRs are above 1 for dermal long-term local route for the exposure scenarios given in the table below

Table 12

RCR$_S$ FOR DERMAL LONG-TERM LOCAL ROUTE				
Population	**Scenario**	**Exposure conentration**	**DNEL$_{eMSCA}$ for Skin Sensitisation**	**RCR**
Industrial workers	Manufacturing – 'contributing scenarios (3), (4), and (9) for PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises or PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated	75 – 100 µg/cm^2	47 µg/cm^2	>2

	facilities'.			
Professional workers	Formulation use – 'contributing scenario (4) for PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)'	47 – 50 µg/cm^2	47 µg/cm^2	>1

With eMSCA's revised DNEL for skin sensitisation, the RCRs are well above 1 for dermal long-term local route for the use of cleaning products with highest concentration of citronellal on the Swedish market as shown in the table below. While calculating these RCRs the eMSCA considered a linear relation to the exposure of citronellal and its concentration in the products.

Table 13

RCR$_S$ FOR DERMAL LONG-TERM LOCAL ROUTE				
Population	**Use**	**Highest conc. in products in the Exposure Scenarios**	**Highest conc. in products reported in the Swedish Product Register**	**RCR (with DNEL$_{eMSCA}$) for the use of products with highest conc. on Swedish market**
Professional workers	Use in cleaning agents – Professional	<1%	>>1%	>5

Important note: "Since sensitisation is essentially systemic in nature, it is important for the purposes of risk management to acknowledge that skin sensitisation may be acquired by other routes of exposure than dermal. There is therefore a need for cautious use of known contact allergens in products to which consumers or workers may be exposed by inhalation" (ECHA Guidance on information requirements and chemical safety assessment, Part E: Risk Characterisation (version 2.0, November 2012)).

7.14. References

Note: The references citing the studies reported in the registration dossier can be found on the ECHA dissemination webpage http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

Lalko, J & Api, A.M. 2008. Citral: Identifying a threshold for induction of dermal sensitization. Regulatory Toxicology and Pharmacology 52 (2008) 62–73.

7.15. Abbreviations

AF Assessment Factor

DNEL Derived No-Effect Level

eMSCA	Evaluating Member State Competent Authority
HRIPT	Human Repeated Insult Patch Test
HMT	Human Maximization Test
LLNA	Local Lymph Node Assay
NOEL	No Observed Effect Level
PROC	Process Category