

## Short review

## RIFM Fragrance Ingredient Safety Assessment, d-Cyclocitronellene acetate, CAS Registry Number 25225-10-9



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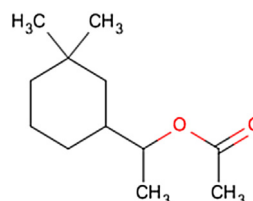
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**CAS Registry Number:** 25225-10-9



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(continued)

**Abbreviation list:****2-Box Model** – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration**AF**- Assessment Factor**BCF**- Bioconcentration Factor**Crete RIFM model**- The Crete RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) compared to a deterministic aggregate approach.**DEREK**- Derek nexus is an *in silico* tool used to identify structural alerts**DST**- Dermal Sensitization Threshold**ECHA**-European Chemicals Agency**EU** – Europe/European Union**GLP**- Good Laboratory Practice**IFRA**- The International Fragrance Association**LOEL**- Lowest Observable Effect Level**MOE**- Margin of Exposure**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition**NA** – North America**NESIL**- No Expected Sensitization Induction Level**NOAEC**- No Observed Adverse Effect Concentration**NOAEL**- No Observed Adverse Effect Level**NOEC**- No Observed Effect Concentration**OECD**- Organisation for Economic Co-operation and Development**OECD TG**- Organisation for Economic Co-operation and Development Testing Guidelines**PBT**- Persistent, Bioaccumulative, and Toxic**PEC/PNEC**- Predicted Environmental Concentration/Predicted No Effect Concentration**QRA**- Quantitative Risk Assessment**REACH**- Registration, Evaluation, Authorisation, and Restriction of Chemicals**RIFM**- Research Institute for Fragrance Materials**RQ**- Risk Quotient**TTC**- Threshold of Toxicological Concern**UV/Vis Spectra**- Ultra Violet/Visible spectra**VCF**- Volatile Compounds in Food**VoU**- Volume of Use**vPvB**- (very) Persistent, (very) Bioaccumulative**WOE** – Weight of Evidence**RIFM's Expert Panel**<sup>\*</sup> concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

<sup>\*</sup>RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

**Summary: The use of this material under current use conditions is supported by the existing information.**

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the suitable read across analog acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7) show that this material is not genotoxic. Data from the suitable read across analog acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7) provided a MOE > 100 for the repeated dose toxicity endpoint. Data on the target material show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The developmental and reproductive toxicity endpoint was completed using 1-cyclohexylethyl butyrate (CAS # 63449-88-7) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 236391-76-7) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

**Human Health Safety Assessment****Genotoxicity:** Not genotoxic.

(RIFM, 2008; RIFM, 2000a,b)

**Repeated Dose Toxicity:** NOAEL = 15 mg/kg/day

(RIFM, 2000a,b)

**Developmental and Reproductive Toxicity:** NOAEL = 1000 and 698 mg/kg/day respectively (RIFM, 1978a,b; ECHA REACH Dossier: reaction mass of (1S,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate, (1R,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate and (1R\*,2'R\*)-(2,6,6-trimethyl-1-cycloheptyloxy carbonyl)methyl propanoate)

**Skin Sensitization:** Not sensitizing

(RIFM, 1981; RIFM, 1982; RIFM, 1977a; RIFM, 1977b; RIFM, 1977c; RIFM, 1977d)

**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic.

(UV spectra, RIFM DB)

**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.**Environmental Safety Assessment****Hazard Assessment:****Persistence:** Screening Level: 2.7 (Biowin 3)

(EpiSuite ver 4.1)

**Bioaccumulation:** Screening Level: 385 L/Kg

(EpiSuite ver 4.1)

**Ecotoxicity:** Critical Ecotoxicity Endpoint: 48 h Algae EC50: 0.474 mg/L

(EpiSuite ver 4.1)

**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards**Risk Assessment:****Screening-Level:** PEC/PNEC (North America and Europe) > 1

(RIFM Framework; Salvito et al., 2002)

**Critical Ecotoxicity Endpoint:** 48 h Algae EC50: 0.474 mg/L

(EpiSuite ver 4.1)

**RIFM PNEC is:** 0.0474 µg/L**•Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: <1

## 1. Identification

1. **Chemical Name:** d-Cyclocitronellene acetate
2. **CAS Registry Number:** 25225-10-9
3. **Synonyms:** d-Cyclocitronellene acetate; Cyclohexanemethanol,  $\alpha$ ,3,3-trimethyl-, acetate;  $\alpha$ ,3,3-Trimethylcyclohexylmethyl acetate; Rosa Musk; CP Acetate; 1-(3,3-Dimethylcyclohexyl)ethyl acetate
4. **Molecular Formula:** C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>
5. **Molecular Weight:** 198.31
6. **RIFM Number:** 1200

## 2. Physical data

1. **Boiling Point:** >204 °C [FMA database], (calculated) 230.13 °C [EPI Suite]
2. **Flash Point:** 191 °F; CC [FMA database]
3. **Log K<sub>ow</sub>:** 4.42 [EPI Suite]
4. **Melting Point:** 13.46 °C [EPI Suite]
5. **Water Solubility:** 7.462 mg/L [EPI Suite]
6. **Specific Gravity:** 0.93 [FMA database]
7. **Vapor Pressure:** 0.04 mm Hg 20 °C [FMA database], 0.0505 mm Hg @ 20 °C [EPI Suite 4.0], 0.0777 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol<sup>-1</sup>cm<sup>-1</sup>)
9. **Appearance/Organooleptic:** A colorless clear liquid with medium floral rose musk fruity geranium odor.\*

\*Retrieved 07/03/13 from: <http://www.thegoodscentscompany.com/data/rw1005121.html>

## 3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95<sup>th</sup> Percentile Concentration in Hydroalcohols:** 0.028% (RIFM, 2015)
3. **Inhalation Exposure\*:** 0.0076 mg/kg/day or 0.62 mg/day (RIFM, 2015)
4. **Total Systemic Exposure\*\*:** 0.0081 mg/kg/day (RIFM, 2015)

\*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015).

\*\*95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015).

## 4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%

## 3. Inhalation: Assumed 100%

## 5. Computational toxicology evaluation

### 1. Cramer Classification: Class I, Low (Expert Judgment)

Expert Judgment	ToxTree v2.6	OECD QSAR Toolbox v3.2
I*	II	I

\*See Appendix below for explanation.

### 2. Analogs Selected:

- a. **Genotoxicity:** Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7)
- b. **Repeated Dose Toxicity:** Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7)
- c. **Developmental and Reproductive Toxicity:** 1-Cyclohexylethyl butyrate (CAS # 63449-88-7); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 236391-76-7)
- d. **Skin Sensitization:** None
- e. **Phototoxicity/Photoallergenicity:** None
- f. **Local Respiratory Toxicity:** None
- g. **Environmental Toxicity:** None

### 3. Read-across Justification: See Appendix below

## 6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

## 7. Natural occurrence (discrete chemical) or Composition (NCS)

d-Cyclocitronellene acetate is not reported to occur in food by the VCF\*.

\*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

## 8. IFRA standard

None.

## 9. REACH dossier

Pre-Registered for 2010; No dossier available as of 12/1/16.

## 10. Summary

### 10.1. Human health endpoint summaries

#### 10.1.1. Genotoxicity

Based on the current existing data, d-cyclocitronellene acetate does not present a concern for genotoxicity.

**10.1.1.1. Risk assessment.** The mutagenic activity of d-cyclocitronellene acetate (CAS # 25225-10-9) was assessed for mutagenic activity in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA were evaluated at concentrations up to 313 µl/plate of d-cyclocitronellene acetate in DMSO (dimethyl sulfoxide) in the presence and absence of metabolic activation. No increase in the frequency of revertant colonies was observed in any of the strains at the concentrations tested (RIFM, 2008). Under the conditions of the study, d-cyclocitronellene acetate is not mutagenic in bacterial reverse mutation study.

There are no studies assessing the clastogenic activity of d-cyclocitronellene. Read across material acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7; see Section 5) was assessed for clastogenicity in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester in DMSO (dimethyl sulfoxide) at concentrations up to 5000 µg/ml and up to 2500 µg/ml in a second experiment, in the presence and absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (RIFM, 2000a,b). Under the conditions of the study, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was considered to be non-clastogenic to cultured human lymphocyte cells, and this can be extended to d-cyclocitronellene acetate.

Based on the available data, d-cyclocitronellene acetate does not present a concern for genotoxic potential.

**Additional References:** RIFM, 2012; RIFM, 1999.

**Literature Search and Risk Assessment Completed on:** 07/03/13.

#### 10.1.2. Repeated dose toxicity

The margin of exposure for d-cyclocitronellene acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

**10.1.2.1. Risk assessment.** There are no repeated dose toxicity data on d-cyclocitronellene acetate. Read across material acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7; see Section 5) has an OECD 407 gavage 28-day dietary subchronic toxicity study conducted in rats which determined the NOAEL to be 545 ppm (equivalent to 44 mg/kg/day for males and 51 mg/kg/day for females), based on reduced body weight gain and clinical chemistry changes (RIFM, 2000a,b).

A default safety factor of 3 was used when deriving a NOAEL from the 28 day or OECD 422/421/407 studies. The safety factor has

been approved by RIFM's Independent Expert Panel\*.

Thus the derived NOAEL for the repeated dose toxicity data is 44/3 or 15 mg/kg/day.

**Therefore, the d-cyclocitronellene acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester NOAEL in mg/kg/day by the total systemic exposure for d-cyclocitronellene acetate, 15/0.0081 or 1852.**

**In addition, the total systemic exposure for d-cyclocitronellene acetate (8.1 µg/kg/day) is below the TTC (30 µg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.**

\*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Additional References:** Bhatia et al., 2008; Belsito et al., 2008; RIFM, 1978a,b.

**Literature Search and Risk Assessment Completed on:** 06/08/16.

#### 10.1.3. Developmental and reproductive toxicity

The margins of exposure for d-cyclocitronellene acetate are adequate for the developmental and reproductive toxicity endpoints at the current level of use.

**10.1.3.1. Risk assessment.** There are no developmental toxicity data on d-cyclocitronellene acetate. Read across material 1-cyclohexylethyl butyrate (CAS # 63449-88-7; see Section 5) has a gavage developmental toxicity study conducted in rats which concluded a NOAEL of 1000 mg/kg/day, based on decreased fetal body weights (RIFM, 1978a,b). There were no teratogenic effects observed even at dosages that caused maternal toxicity. Therefore, the d-cyclocitronellene acetate MOE for the developmental toxicity endpoint can be calculated by dividing the 1-cyclohexylethyl butyrate NOAEL in mg/kg/day by the total systemic exposure for d-cyclocitronellene acetate, 1000/0.0081 or 123457.

There are no reproductive toxicity data on d-cyclocitronellene acetate. Read across material acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7; see Section V) has an enhanced OECD 421 dietary reproduction/developmental toxicity screening test conducted in rats which determined the NOAEL for reproductive toxicity to be 11000 ppm (equivalent to 698 mg/kg/day for the males, 804–1467 mg/kg/day for the main reproductive toxicity phase females, and 737 mg/kg/day for the toxicity phase females), the highest dosage tested (ECHA REACH Dossier: reaction mass of (1S,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate, (1R,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate and (1R\*,2'R\*)-(2,6,6-trimethyl-1-cycloheptyloxy carbonyl)methyl propanoate, accessed 06/17/14). The most conservative NOAEL of 698 mg/kg/day was selected for this safety assessment. **Therefore, the d-cyclocitronellene acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester NOAEL in mg/kg/day by the total systemic exposure for d-cyclocitronellene acetate, 698/0.0081 or 86173.**

**In addition, the total systemic exposure for d-cyclocitronellene acetate (8.1 µg/kg/day) is below the TTC (30 µg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoints.**

**Additional References:** Bhatia et al., 2008; Belsito et al., 2008; RIFM, 1978a,b.

**Literature Search and Risk Assessment Completed on:** 06/17/14.

#### 10.1.4. Skin sensitization

Based on the existing data, d-cyclocitronellene acetate does not present a concern for skin sensitization.

**10.1.4.1. Risk assessment.** Based on the available data, d-cyclocitronellene acetate does not present a concern for skin sensitization. d-Cyclocitronellene acetate is not predicted to be reactive to skin proteins and therefore would present a low concern for skin sensitization (Roberts et al., 2007; Toxtree 2.5.0; OECD Toolbox v3.3). In a guinea pig maximization test and in human confirmatory studies, no results indicative of a sensitization potential were reported (RIFM, 1981; RIFM, 1982; RIFM, 1977a; and RIFM, 1977b; RIFM, 1977c; and RIFM, 1977d).

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 07/03/13.

#### 10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, d-cyclocitronellene acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

**10.1.5.1. Risk assessment.** There are no phototoxicity studies available for d-cyclocitronellene acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity,  $1000 \text{ L mol}^{-1} \text{ cm}^{-1}$  (Henry et al., 2009). Based on lack of absorbance, d-cyclocitronellene acetate does not present a concern for phototoxicity or photoallergenicity.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 07/19/16.

#### 10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, d-cyclocitronellene acetate exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

**10.1.6.1. Risk assessment.** There are no inhalation data available on d-cyclocitronellene acetate. Based on the Creme RIFM model, the inhalation exposure is 0.62 mg/day. This exposure is 2.3 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 6/13/2016.

### 10.2. Environmental endpoint summary

#### 10.2.1. Screening-level assessment

A screening level risk assessment of d-cyclocitronellene acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk using exposure scenarios developed for North America

and Europe. In Tier 1, only the material's volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, d-cyclocitronellene acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify d-cyclocitronellene acetate as possibly persistent or bio-accumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bio-accumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

#### 10.2.2. Risk assessment

Based on current Volume of Use (2011), d-cyclocitronellene presents a risk to the aquatic compartment in the screening level assessment.

#### 10.2.3. Key studies

**10.2.3.1. Biodegradation.** No data available.

**10.2.3.2. Ecotoxicity.** No data available.

**10.2.3.3. Other available data.** d-Cyclocitronellene has been pre-registered for REACH with no additional data at this time.

### 11. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in  $\mu\text{g/L}$ ).

Endpoints used to calculate PNEC are underlined.



	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level (Tier 1)	<u>2.098 mg/l</u>			1,000,000	0.00209 µg/l	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	1.02 mg/l	1.636 mg/l	<u>0.474 mg/l</u>	10,000	0.0474 µg/l	Esters
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	1.087mg/l	0.772 mg/l	1.450 mg/l			Neutral Organic

Exposure information and PEC calculation (following RIFM Framework: [Salvito et al., 2002](#)).

Exposure	Europe (EU)	North America (NA)
Log K <sub>ow</sub> used	4.42	4.42
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt;1</b>	<b>&lt;1</b>

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

**The RIFM PNEC is 0.0474 µg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.**

**Literature Search and Risk Assessment Completed on: 07/03/13.**

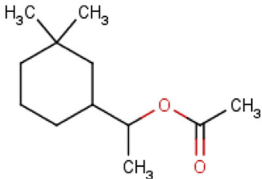
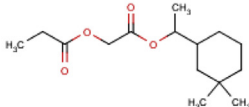
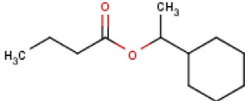
## 12. Literature Search\*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>
- **NTP:** [http://tools.niehs.nih.gov/ntp\\_tox/index.cfm](http://tools.niehs.nih.gov/ntp_tox/index.cfm)
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PUBMED:** <http://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <http://toxnet.nlm.nih.gov/>

- **IARC** (<http://monographs.iarc.fr/>):
- **OECD SIDS:** <http://www.chem.unep.ch/irptc/sids/oecd/sids/sidspub.html>
- **EPA Actor:** <http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7>
- **US EPA HPVIS:** <http://www.epa.gov/hpv/hpvis/index.html>
- **US EPA Robust Summary:** <http://cfpub.epa.gov/hpv-s/>
- **Japanese NITE:** <http://www.safe.nite.go.jp/english/db.html>
- **Japan Existing Chemical Data Base:** [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)
- **Google:** <https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4>

\*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

## Appendix

	Target Material	Read across Material	
Principal Name	d-Cyclocitronellene acetate	Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester	1-Cyclohexylethyl butyrate
CAS No.	25225-10-9	236391-76-7	63449-88-7
Structure			
3D Structure	<a href="http://www.thegoodscentscompany.com/opl/25225-10-9.html">http://www.thegoodscentscompany.com/opl/25225-10-9.html</a>	<a href="http://www.thegoodscentscompany.com/opl/236391-76-7.html">http://www.thegoodscentscompany.com/opl/236391-76-7.html</a>	<a href="http://www.thegoodscentscompany.com/opl/63449-88-7.html">http://www.thegoodscentscompany.com/opl/63449-88-7.html</a>
Read-across endpoint		<ul style="list-style-type: none"> <li>• Genotox</li> <li>• Repeated Dose</li> <li>• Devel/Repro</li> </ul>	<ul style="list-style-type: none"> <li>• Devel/Repro</li> </ul>
Molecular Formula	C <sub>12</sub> H <sub>22</sub> O <sub>2</sub>	C <sub>15</sub> H <sub>26</sub> O <sub>4</sub>	C <sub>12</sub> H <sub>22</sub> O <sub>2</sub>
Molecular Weight	198.31	270.37	198.31
Melting Point (°C, EPISUITE)	13.46	5.19	7.96
Boiling Point (°C, EPISUITE)	230.13	294.03	244.94
Vapor Pressure	10.36	0.3573	4.746

	Target Material	Read across Material	
(Pa@ 25°C, EPISUITE)			
Log Kow (KOWWIN v1.68 in EPISUITE)	4.42	4.45	4.53
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	7.462	2.856	5.997
J <sub>max</sub> (mg/cm <sup>2</sup> /h, SAM)	13.38676759	1.593971953	21.45262384
Henry's Law (Pa·m <sup>3</sup> /mol, Bond Method, EPISUITE)	100.321883	2.244349	100.321883
Similarity (Tanimoto score) <sup>1</sup>		71%	61%
<i>In silico Results for target and analogs</i>			
<b>Genotoxicity</b>			
DNA binding by OASIS v 1.1 QSAR Tool Box (3.1)	<ul style="list-style-type: none"> <li>•Schiff base formers</li> <li>•Schiff base formers &gt;&gt; Direct acting Schiff base formers</li> <li>•Schiff base formers &gt;&gt; Direct acting Schiff base formers &gt;&gt; Specific Acetate Esters</li> <li>•SN1</li> </ul>	•No alert found	



	Target Material	Read across Material	
	<ul style="list-style-type: none"> <li>•SN1 &gt;&gt; Carbenium ion formation</li> <li>•SN1 &gt;&gt; Carbenium ion formation &gt;&gt; Specific Acetate Esters</li> <li>•SN2</li> <li>•SN2 &gt;&gt; Acylating agents</li> <li>•SN2 &gt;&gt; Acylating agents &gt;&gt; Specific Acetate Esters</li> <li>•SN2 &gt;&gt; SN2 at sp<sup>3</sup>-carbon atom</li> <li>•SN2 &gt;&gt; SN2 at sp<sup>3</sup>-carbon atom &gt;&gt; Specific Acetate Esters</li> </ul>		
DNA binding OECD	•No alert found	•No alert found	
Carcinogenicity (genotox and non-genotox) alerts by ISS	•No alert found	•No alert found	
DNA alerts for Ames, MN, CA by OASIS v 1.1	•No alert found	•No alert found	
In-vitro Mutagenicity (Ames test) alerts by ISS	•No alert found	•No alert found	

	Target Material	Read across Material	
<b>In-vivo mutagenicity</b> <b>(Micronucleus) alerts by ISS</b>	•H-acceptor-path3-H-acceptor	•H-acceptor-path3-H-acceptor	
<b>Oncologic Classification</b>	•Not classified	•Not classified	
<b>Repeated Dose Toxicity</b>			
<b>Repeated dose (HESS)</b>	Not categorized	Not categorized	
<b>Developmental and Reproductive Toxicity</b>			
<b>ER binding (OECD)</b>	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
<b>Developmental toxicity model (CAESAR v2.1.6)</b>	Toxicant (moderate reliability)	NON-Toxicant (moderate reliability)	NON-Toxicant (moderate reliability)
<b>Metabolism</b>			
<b>Rat liver S9 metabolism simulator (OECD)</b>	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

<sup>1</sup> Values calculated using JChem with FCFP4 1024 bits fingerprint. J. Chem. Inf. Model. 2010, 50: 742 (Rogers and Hahn, 2010).

## Summary

There are insufficient toxicity data on d-cyclocitronellene acetate (RIFM # 1200, CAS # 25225-10-9). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physico-chemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

## Methods:

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The J<sub>max</sub> were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.2) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.2) (OECD, 2012).
- Developmental toxicity was estimated using CAESAR (v2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.2) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.2) (OECD, 2012).

## Conclusion/Rationale

- For Target material d-Cyclocitronellene acetate (CAS # 25225-10-9), Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl) ethyl ester (CAS # 236391-76-7) was used as a read across analog for genotoxicity, reproductive and developmental toxicity and repeated dose toxicity endpoints and 1-Cyclohexylethyl butyrate (CAS 3449-88-7) was used as a read across analog for reproductive and developmental toxicity endpoints.
  - The target substance and the read across analog are structurally similar and belong to the structural class of aliphatic cyclic esters.
  - The target substance and the read across analog share a cyclocitronellal alcohol portion.
  - The key difference between the target substance and the read across analog is that the read across analog Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester has diester functionality while and read across analog 1-Cyclohexylethyl butyrate has butyric acid portion compared to acetic acid poriton of the target. This structure difference between the target substance and the read across analog does not affect consideration of the toxic endpoint.
  - Similarity between the target substance and the read across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxic endpoint.
  - The physical chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J<sub>max</sub>, which estimates skin absorption. The J<sub>max</sub> values translate to 80% skin aborption for the target

substance, 40% absorption for Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester and 80% absorption for 1-Cyclohexylethyl butyrate. While percentage skin absorption estimated from  $J_{\max}$  values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the  $J_{\max}$  of the target substance and the appropriate read across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.

- According to the QSAR OECD Toolbox (V3.4), the target material has an alert of Schiff base formation while the read across analog Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not have that alert. On the contrary, the read across analog has path 3 H acceptor alert by ISS model for in-vivo mutagenicity which the target lack. Other genotoxicity alerts are negative for both of the substances. The data described in the genotoxicity section above shows that the read across analog does not pose a concern for genetic toxicity. Therefore the alerts will be overridden by the data.
- According to CAESAR model for developmental toxicity, the target is predicted to be a toxicant with moderate reliability while the read across analogs are predicted to be non-toxicants with moderate reliability. ER binding alert is negative for the target as well as the read across analog. The data described in the developmental toxicity section shows that the margin of exposure for read across analogs is adequate at the current level of use. Therefore the alerts will be ignored.
- The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural differences between the target material and the read across analog do not affect consideration of the toxic endpoints.

#### Explanation of Cramer Class:

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

- Q1. Normal constituent of the body? **No**  
 Q2. Contains functional groups associated with enhanced toxicity? **No**  
 Q3. Contains elements other than C,H,O,N, divalent S? **No**  
 Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**  
 Q6. Benzene derivative with certain substituents? **No**  
 Q7. Heterocyclic? **No**  
 Q16. Common terpene? **No**  
 Q17. Readily hydrolysed to a common terpene? **Yes**  
 Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? **No** Class Low (Class I) 'Residue 1'  
 Q19. Open chain? **Yes** 'Residue 2'  
 Q20. Aliphatic with some functional groups? **Yes** 'Residue 2'  
 Q21.3 or more different functional groups? **No** 'Residue 2'  
 Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features

generally thought to be associated with some enhanced toxicity)? **No** Class Low (Class I) 'Residue 2'

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2017.03.004>.

#### Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2017.03.004>.

#### References

- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renkers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G., Tagami, H., 2008. A toxicologic and dermatologic assessment of cyclic acetates when used as fragrance ingredients. *Food Chem. Toxicol.* 46 (12S), S1–S27.
- Bhatia, S.P., Letizia, C.S., Api, A.M., 2008. Fragrance material review on d-cyclocitronellene acetate. *Food Chem. Toxicol.* 46 (12S), S48–S51.
- Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR toolbox and expert judgment. *Regul. Toxicol. Pharmacol.* 71 (1), 52–62, 73(3).
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. *Chem. Central J.* 4 (Suppl. 1), S4.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. *Food Cosmet. Toxicol.* 16 (3), 255–276.
- ECHA REACH Dossier: reaction mass of (1S,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate, (1R,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate and (1R\*,2'R\*)-(2,6,6-trimethyl-1-cycloheptyloxy)carbonyl]methyl propanoate: <https://echa.europa.eu/home>.
- Essential Estimation Programs Interface (EPI) Suite™ (version 4.1) [Software]. (Copyright 2000–2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm> Research, 20(6), 482–487.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.
- OECD, 2012. The OECD QSAR Toolbox, V. 3.1. <http://www.qsartoolbox.org/>.
- RIFM (Research Institute for Fragrance Materials, Inc), 1977a. Sensitization Study with D-cyclocitronellene Acetate in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 53079. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1977b. Repeated Insult Patch Test with D-cyclocitronellene Acetate. Unpublished report from International Flavors and Fragrances. RIFM report number 53080. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1977c. Repeated Insult Patch Test with D-cyclocitronellene Acetate. Unpublished report from International Flavors and Fragrances. RIFM report number 53081. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1977d. Repeated Insult Patch Test with D-cyclocitronellene Acetate. Unpublished report from International Flavor and Fragrances. RIFM report number 53082. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1978a. Four-week Oral Toxicity Study with 1-cyclohexylethyl Butyrate. Unpublished report from International Flavors and Fragrances. RIFM report number 50431. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1978b. Teratology Study of 1-cyclohexylethyl Butyrate in Rats. Unpublished report from International Flavors and Fragrances. RIFM report number 50432. RIFM, Woodcliff Lake, NJ, USA.

- RIFM (Research Institute for Fragrance Materials, Inc), 1981. Screening Test for Delayed Contact Hypersensitivity with D-cyclocitronellene Acetate in the Albino Guinea-pig. RIFM report number 1771. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1982. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1643. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1999. Acetic Acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl Ester (Romandolide): Reverse Mutation Assay "Ames Test" Using *Salmonella typhimurium* and *Escherichia coli* (Addendum Attached) Unpublished report from Firmenich Incorporated. RIFM report number 64189. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2000a. Acetic Acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl Ester (Romandolide): in Vitro Mammalian Chromosome Aberrations Test in Cultured Human Lymphocytes. Unpublished report from Firmenich Incorporated. RIFM report number 64191. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2000b. Acetic Acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl Ester (Romandolide): Four-week Repeated Toxicity Study by Oral Route (Dietary Admixture) in Rats. Unpublished report from Firmenich Incorporated. RIFM report number 64194. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2008. Mutagenicity Test of Delta-cyclocitronellene Acetate Using Microorganisms. Unpublished report from International Flavors and Fragrances. RIFM report number 54403. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2012. Acetic Acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl Ester (Romandolide): in Vitro HPRT Mutation Test Using Chinese Hamster Ovary Cells. Unpublished report from Firmenich Incorporated. RIFM report number 64168. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials), 2015. Use Level Survey, February, 2015.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem. Res. Toxicol.* 20 (7), 1019–1030.
- Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* 50 (5), 742–754.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Contact Dermat.* 21 (6), 1301–1308.
- Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. *Food Chem. Toxicol.* 74 (12), 164–176.
- USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, V. 4.11. United States Environmental Protection Agency, Washington, DC, USA.