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Short review

RIFM fragrance ingredient safety assessment, *l*-Cyclocitronellene formate, CAS Registry Number 25225-08-5

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1. Identification

1. **Chemical Name:** *l*-Cyclocitronellene formate
2. **CAS Registry Number:** 25225-08-5
3. **Synonyms:** *l*-Cyclocitronellene formate; Cyclohexanemethanol,.α.,3,3-trimethyl-, formate; a,3,3-Trimethylcyclohexylmethyl formate; CP Formate; Aphermate; 1-(3,3-Dimethylcyclohexyl)ethyl formate
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.28
6. **RIFM Number:** 1157

2. Physical data

1. **Boiling Point:** 212.97 °C [EPI Suite]
2. **Flash Point:** 74 °C [GHS], 165 °F; CC [FMA]
3. **Log K_{OW}:** Log Pow = <1.1–4.3 [IFF, 2012q], 3.88 [EPI Suite]
4. **Melting Point:** 11 °C [EPI Suite]
5. **Water Solubility:** 25.73 mg/L [EPI Suite]
6. **Specific Gravity:** 0.937 [FMA]
7. **Vapor Pressure:** 0.125 mmHg @ 20 °C [EPI Suite 4.0], 0.1 mm Hg 20C [FMA], 0.188 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^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium, woody, fresh, herbal, seashore, fruity, apple odor.*

*http://www.thegoodscentscompany.com/data/rw1017321.html#toorgano, retrieved 10/28/2015.

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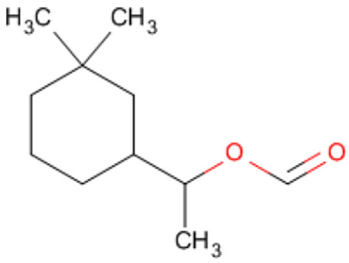
Version: 011017. This version replaces any previous versions.
Name: *l*-Cyclocitronellene formate
CAS Registry Number: 25225-08-5



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
Creme RIFM model-The Creme 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* 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).
*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 conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analogue *d*-cyclocitronellene acetate (CAS # 25225-10-9) show that this material does not have the potential for skin sensitization. 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 repeated dose and reproductive toxicity endpoints were completed using acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7) as a suitable read across analogue, which provided a MOE > 100. The developmental 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 will be 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, 2006; RIFM, 2012a)
Repeated Dose Toxicity: NOAEL = 15 mg/kg/day (RIFM, 2000)
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-cycloheptyloxycarbonyl)methyl propanoate)
Skin Sensitization: Not a sensitization concern. (RIFM, 1981; RIFM, 1972; RIFM, 1971)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)

(*continued*)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 48% (day 120, OECD 301D)	(RIFM, 2013)
Bioaccumulation: Screening Level: 167 L/kg	(EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 72 h Algae EC50: 2.0 mg/L	(RIFM, 2012b)
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: 72 h Algae EC50: 2.0 mg/L	(RIFM, 2012c)
RIFM PNEC is: 2.0 μg/L	
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe: <1	

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.086% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00059 mg/kg/day or 0.044 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0029 mg/kg/day (RIFM, 2016)

*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:** Data not available – not considered.
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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2. **Analogs Selected:**
a. **Genotoxicity:** None
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); acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7)
d. **Skin Sensitization:** *d*-Cyclocitronellene acetate (CAS # 25225-10-9)
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)

L-Cyclocitronellene formate 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 1/10/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, *l*-cyclocitronellene formate does not present a concern for genotoxicity.

10.1.2. Risk assessment

The mutagenic activity of *l*-cyclocitronellene formate was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *S. typhimurium* strains TA100, TA1535, TA98 and TA1537 and *E. coli* strain WP2uvrA were treated with *l*-cyclocitronellene formate in DMSO (dimethyl sulfoxide) at concentrations of 4.88, 19.5, 78.1, 313, 1250 and 5000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies were observed

compared to the negative control (RIFM, 2006). Under the conditions of the study, *l*-cyclocitronellene formate was considered not mutagenic in the Ames assay.

The clastogenic activity of *l*-cyclocitronellene formate was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD 487. Human peripheral blood lymphocytes were treated with *l*-cyclocitronellene formate in DMSO in two independent experiments: dose levels for the first experiment ranged from 3.6 μg/ml to 1841 μg/ml for 4 h in the presence and absence of S9 mix and dose levels for the second experiment ranged from 6.25 μg/ml to 500 μg/ml for 20 h in the absence of S9 mix. L-Cyclocitronellene formate did not induce binucleated cells with micronuclei when tested up to the maximum dose in either the non-activated or S9 activated test systems (RIFM, 2012d). Under the conditions of the study, *l*-cyclocitronillene formate was considered non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, *l*-cyclocitronellene formate does note present a concern for genotoxic potential.

Additional References: RIFM, 2012e,f.

Literature Search and Risk Assessment Completed on: 2/3/16.

10.1.3. Repeated dose toxicity

The margin of exposure for *l*-cyclocitronellene formate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on *l*-cyclocitronellene formate. 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, 2000).

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 *l*-cyclocitronellene formate 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 *l*-cyclocitronellene formate, 15/0.0029 or 5172.

In addition, the total systemic exposure for *l*-cyclocitronellene formate (2.9 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: 5/19/2016.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for *l*-cyclocitronellene formate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on *l*-cyclocitronellene formate. 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 *l*-cyclocitronellene formate 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 *l*-cyclocitronellene formate, 1000/0.0029 or 344828.**

There are no reproductive toxicity data on *l*-cyclocitronellene formate. Read across material acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7) 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 reprotoxicity 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-cycloheptyloxycarbonyl)methyl propanoate, accessed 06/17/14). The most conservative NOAEL of 698 mg/kg/day was selected for this safety assessment. **Therefore, the *l*-cyclocitronellene formate 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 *l*-cyclocitronellene formate, 698/0.0029 or 237586.**

In addition, the total systemic exposure for *l*-cyclocitronellene formate (2.9 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoint at the current level of use.

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

Literature Search and Risk Assessment Completed on: 5/19/2016.

10.1.7. Skin sensitization

Based on existing data and read across to *d*-cyclocitronellene acetate (CAS # 25225-10-9), *l*-cyclocitronellene formate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data and read across to *d*-cyclocitronellene acetate (CAS # 25225-10-9; see Section 5), *l*-cyclocitronellene formate does not present a concern for skin sensitization. L-Cyclocitronellene formate and D-cyclocitronellene acetate are not predicted to react directly with skin proteins (Toxtree 2.6.6; OECD toolbox v3.3). No animal studies are available on *l*-cyclocitronellene formate however, in a guinea pig maximization test, read across material *d*-cyclocitronellene acetate was found to be non-sensitizing (RIFM, 1981). In a human repeat insult patch test (HRIPT), *l*-cyclocitronellene formate did not induce sensitization reactions at 4% (3101 μg/cm²) (RIFM, 1971) or 5% (3876 μg/cm²) (RIFM, 1972). In a human maximization test conducted on 22 subjects, no reactions indicative of sensitization were observed with 10% *l*-cyclocitronellene formate (6900 μg/cm^2) (RIFM, 1982). Moreover, no results indicative of sensitization potential were reported with read across material *d*-cyclocitronellene acetate (RIFM, 1976; RIFM, 1982; RIFM, 1977a; RIFM, 1977b; RIFM, 1977c; RIFM, 1977d). Based on weight of evidence from available human data and read across material, *l*-cyclocitronellene formate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/10/2015.

10.1.9. Phototoxicity/photoallergenicity

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

10.1.10. Risk assessment

There are no phototoxicity studies available for *l*-cyclocitronellene formate 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 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, *l*-cyclocitronellene formate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/20/16.

10.1.11. Local Respiratory Toxicity

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

10.1.12. Risk assessment

There are no inhalation data available on *l*-cyclocitronellene formate. Based on the Creme RIFM model, the inhalation exposure is 0.044 mg/day. This exposure is 31.8 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: 05/31/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of *l*-cyclocitronellene formate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. 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, *l*-cyclocitronellene formate 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 *l*-cyclocitronellene formate as either being possibly persistent nor bioaccumulative 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 bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.3. Biodegradation

RIFM, 2007: The ready biodegradability over a period of 28 days with activated sludge bacteria was conducted according to the OECD 301C guidelines. Under the conditions of this study, one of the components of the test material increased, and the rest of the components of the test material were changed into the formic acid and the several unknown converted products. The formic acid seemed to be converted by the microorganisms, whereas the increased component of the test material and the several unknown converted products were not biodegraded by microorganisms and remained.

RIFM, 2013: Biodegradability of the test material was determined by the Closed Bottle Test according to the OECD 301D method. Duplicate bottles of day 21 and 28 were also measured on day 90 and 120. Oxygen concentrations in the bottles at day 90 and 120 were reported along with control bottles. The biodegradation percentages of the test material at day 90 and 120 were 27 and 48, respectively. A biodegradation percentage of 61 was found when only using the oxygen concentrations from one of the 90 and 120 day test bottles (90 day-5.4% and 120 day-4.5%).

RIFM, 2012a: The ready biodegradability of the test material was determined in the Closed Bottle test according to the OECD 301D method. Under the conditions of the study, biodegradation of 23% was observed after 60 days.

10.2.4. Ecotoxicity

RIFM, 2012b: An algae growth inhibition test was conducted according to the OECD 201 method. The 72 h EC50 for growth rate reduction exceeded a TWA (time weighed average) concentration of 7.1 mg/L, being the average measured concentration in a WAF prepared at a loading rate of 100 mg/L. The EC50 for yield inhibition based on TWA concentrations was 2.0 mg/L.

RIFM, 2012c: A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 method. The 48 h EC50 was reported to be 7.7 mg/L.

RIFM, 2012d: A fish (Carp) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96 h LC50 was reported to be 8.0 mg/L.

10.2.5. Other available data

L-Cyclocitronellene formate has been pre-registered for REACH with no additional data at this time.

10.2.6. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.480 mg/L			1,000,000	0.00248 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.979 mg/L	3.366mg/L	1.064 mg/L	10,000	0.1064 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.133 mg/L	3.115 mg/L	3.224 mg/L			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	8.0 mg/l					
Daphnia		7.7 mg/l				
Algae		2.0 mg/l		1000	2.0 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.3	4.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 2.0 µg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/17/15.

11. 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
- **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/oecdsids/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
- **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 A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.02.035.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.02.035.

Appendix

Methods:

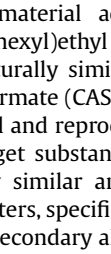
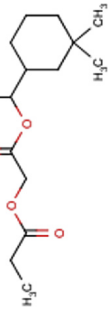
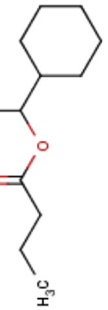
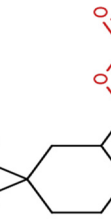
- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- Jmax 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 generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

Summary:

There are insufficient toxicity data on *l*-cyclocitronellene formate (CAS # 25225-08-5). Hence *in-silico* evaluation was conducted to determine suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7), 1-cyclohexylethyl butyrate (CAS # 63449-88-7) and d-cyclocitronellene acetate (CAS # 25225-10-9) were identified as a proper read across materials with data for their respective toxicity endpoints.

12. Conclusion/Rationale

- Read across material acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7) could be used as structurally similar read across analogue for *l*-cyclocitronellene formate (CAS # 25225-08-5) for the repeated dose, developmental and reproductive toxicity endpoints.
  - ○ The target substance and the read across analogue are structurally similar and belong to the structural class of aliphatic esters, specifically, esters/alkyl cyclic alcohol simple acid ester/secondary alcohol metabolite/saturated.
  - ○ The key difference between the target substance and the read across analogue is that the target is a formate, while the analogue has two ester groups. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - ○ The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the cyclocitronellene formate fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological endpoint perspective.

	Target material	Read across material	Read across material	Read across material
Principal Name	*l*-Cyclocitronellene formate	Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester	1-Cyclohexylethyl butyrate	*d*-Cyclocitronellene acetate
CAS No.	25225-08-5	236391-76-7	63449-88-7	25225-10-9
Structure				
Similarity (Tanimoto score)	1	0.574	0.712	0.896
Read across endpoint		• Repeated dose, • Developmental and Reproductive	• Developmental and Reproductive	• Skin sensitization
Molecular Formula	$C_{11}H_{20}O_2$	$C_{15}H_{26}O_4$	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$
Molecular Weight	184.28	270.37	198.31	198.31
Melting Point (°C, EPISUITE)	11.00	5.19	7.96	13.46
Boiling Point (°C, EPISUITE)	212.97	294.03	244.94	230.13
Vapor Pressure (Pa @ 25 °C, EPISUITE)	25	0.3573	4.746	10.4
Log Kow (KOWWIN v1.68 in EPISUITE)	3.88	4.45	4.53	4.42

(continued on next page)

(*continued*)

	Target material	Read across material	Read across material	Read across material
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	25.73	2.856	5.997	7.462
J_{max} (mg/cm^2/h, SAM)	2.836125	1.593,971,953	21.45,262,384	0.980492
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.37E+002	2.244349	100.321883	1.00E+002
Genotoxicity				
DNA binding (OASIS v 1.1 QSAR Toolbox 3.1)	• No alert found	• No alert found	• No alert found	• AN2, SN1, SN2
DNA binding by OECD QSAR Toolbox (3.1)	• No alert found	• No alert found	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• Non carcinogen (moderate reliability)	• Non carcinogen (low reliability)	• No alert found
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found	• No alert found
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found
In-vivo mutagenicity (Micronucleus) alerts by ISS	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor	• No alert found	• H-acceptor-path3-H-acceptor
Oncologic Classification	• Aldehyde type compounds	• Not classified	• Not classified	• Not classified
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Not categorized	• Not categorized
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.1)	• Non binder, without OH or NH_2 group	• Non binder, without OH or NH_2 group	• Non binder, without OH or NH_2 group	• Non binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (low reliability)	• Non toxicant (low reliability)	• Non toxicant (low reliability)	• Toxicant (moderate reliability)
Sensitization				
Protein binding by OASIS v1.1	• No alert found	• SN2 Reaction	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• SN2 Reaction	• No alert found	• No alert found
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• SN2 reaction	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Sensitizer (good reliability)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism				
OECD QSAR Toolbox (3.1)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4
Rat liver S9 metabolism simulator	• 10 metabolites from Rat S9 simulator. • Formic acid and formats, aldehydes, Schiff base formation.	• 11 metabolites from Rat S9 simulator. • Formic acid and formats, aldehydes, Schiff base formation, carboxylic acid (Hepatotoxicity) alert	• 12 metabolites from Rat S9 simulator. • Formic acid and formats, aldehydes, Schiff base formation, carboxylic acid (Hepatotoxicity) alert. Valproic acid (Hepatotoxicity) alert.	• 10 metabolites from Rat S9 simulator. • Aldehydes, esters, Schiff base formation, SN2.

○ The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for repeated dose, developmental and reproductive toxicity endpoints.

○ According to the QSAR OECD Toolbox (V3.4), structural alerts for repeated dose, developmental and reproductive toxicity endpoints are consistent between the target substance and the read across analogue as seen in the table above.

○ The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.

○ The structural alerts for repeated dose, developmental and reproductive toxicity endpoints are consistent between the metabolites of the read across analogue and the target substance.

○ The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

- Read across material 1-cyclohexylethyl butyrate (CAS # 63449-88-7) could be used as a structurally similar read across analogue for *l*-cyclocitronellene formate (CAS # 25225-08-5) for the developmental and reproductive toxicity endpoint.

○ The target substance and the read across analogue are structurally similar and belong to the structural class of aliphatic esters, specifically, esters/alkyl cyclic alcohol simple acid ester/secondary alcohol metabolite/saturated.

○ The key difference between the target substance and the read across analogue is that the target is a formate, while the read across analogue is a butyrate and does not have a dimethyl group in the cyclohexyl ring. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.

○ The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the cyclocitronellene formate fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevent from a toxicological endpoint perspective.

○ The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for developmental and reproductive toxicity endpoint.

○ According to the QSAR OECD Toolbox (V3.4), structural alerts for developmental and reproductive toxicity endpoint are consistent between the target substance and the read across analogue as seen in the table above.

○ The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.

○ The structural alerts for developmental and reproductive toxicity endpoint are consistent between the metabolites of the read across analogue and the target substance.

○ The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

- Read across material *d*-cyclocitronellene acetate (CAS # 25225-10-9) could be used as a structurally similar read across analogue for *l*-cyclocitronellene formate (CAS # 25225-08-5) for the skin sensitization endpoint.

○ The target substance and the read across analogue are structurally similar and belong to the structural class of esters.

○ The key difference between the target substance and the read across analogue is that the read across is an acetate compared to target which is a formate. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.

○ The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 1-(3,3-dimethylcyclohexyl)ethyl fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevent from a toxic endpoint perspective.

○ The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the skin sensitization endpoint.

○ According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin sensitization endpoint are consistent between the target substance and the read across analogue as seen in the table above.

○ The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.

○ The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read across analogue and the target substance.

○ The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

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