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Short Review

RIFM fragrance ingredient safety assessment, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester, CAS Registry Number 236391-76-7

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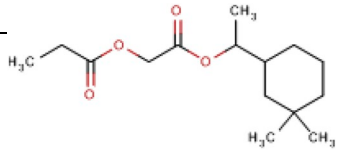
Name: Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester
CAS Registry Number: 236391-76-7



Abbreviation/Definition 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, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice

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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
NOEL - No Observed Effect Level
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
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as 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 includes 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 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., 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 endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety 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 with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester is not genotoxic. Data on acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog *d*-cyclocitronellene acetate (CAS # 25225-10-9) show that there are no safety concerns for acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl) ethyl ester for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1999c; RIFM, 2000d)

Repeated Dose Toxicity: NOAEL = 287 mg/kg/day. (ECHA 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; ECHA, 2013)

Reproductive Toxicity: Developmental toxicity NOAEL = 737 mg/kg/day. Fertility: NOAEL = 698 mg/kg/day. (ECHA 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; ECHA, 2013)

Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use. (RIFM, 1999d; RIFM, 2011)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic (UV Spectra, RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 68% (OECD 301D) (RIFM, 2000i)

Bioaccumulation:

Screening-level: 403 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: 96-hour Algae EC50: 0.615 mg/L (ECOSAR; US EPA, 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: 96-hour Algae EC50: 0.615 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0615 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

1. Identification

1. **Chemical Name:** Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester
2. **CAS Registry Number:** 236391-76-7
3. **Synonyms:** Romandolide; Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester
4. **Molecular Formula:** $C_{15}H_{26}O_4$
5. **Molecular Weight:** 270.36
6. **RIFM Number:** 6437
7. **Stereochemistry:** No stereoisomer specified. Two stereocenters present and 4 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 572 ± 1 K @ 100.63–100.78 kPa (RIFM, 1999a)
2. **Flash Point:** 152 °C (GHS), 152 ± 2 °C (RIFM, 1999b)
3. **Log K_{ow}:** log 10 Pow 4.74 to 4.79 (RIFM, 1999a)
4. **Melting Point**: Not Available
5. **Water Solubility:** 1.09 × 10(-2) of sol. @ 20.0 ± 0.5 °C (RIFM, 1999a)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.053 ± 0.008 Pa at 20 C (RIFM, 2000c), 0.000741 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium musk, ambrette odor*

*http://www.thegoodscentscompany.com/data/rw1612281.html#toorgano, retrieved 7/30/2015.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.017% (RIFM, 2015)
2. **Inhalation Exposure*:** 0.0027 kg/day or 0.20 mg/day (RIFM, 2015)
3. **Total Systemic Exposure**:** 0.031 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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; Safford et al., 2017; and Comiskey et al., 2017).

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 v 2.6	OECD QSAR Toolbox v 3.2
I*	II	I

*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). See the Appendix below for further details.

2. Analogs Selected
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   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)

Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester is not reported to occur in foods 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. REACH dossier

Available; accessed 07/30/2015.

9. Conclusion

The existing information supports the use of this material as described in this safety assessment.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1999c). Under the conditions of the study, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was not mutagenic in the Ames test.

The clastogenicity of acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was assessed 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 at concentrations up to 5000 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 2000d). Under the conditions of the study, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was considered to be non-clastogenic to human/mammalian cells.

Based on the data available, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not present a concern for genotoxic potential.

Additional References: RIFM, 2012.

Literature Search and Risk Assessment Completed On: 06/13/19.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester. An OECD TG 408 and GLP-compliant dietary study was conducted on groups of 10 rats/sex/dose. The animals were fed diets containing the test material at concentrations of 0, 500, 5000, and 11000 ppm for 90 days. These concentrations were equal to 0, 29, 287, and 657 mg/kg/day in males and 0, 37, 351, and 781 mg/kg/day in females. Recovery groups of 5 rats/sex/day were maintained for 5 additional weeks after the end of treatment duration. No treatment-related mortality or clinical signs of toxicity were reported at any dose levels during the study. Bodyweight gain in both sexes was significantly lower in the high-dose group and continued to be lower than the control group following the recovery period. However, food and water consumption were not altered throughout the study. In males of the mid- and high-dose groups, dose-dependent increases in kidney weights were reported during the treatment and recovery periods. The increased kidney weights were accompanied by the increased presence of granular casts, hyaline droplets, and α-2u-globulin protein. The presence of the α-2u-globulin protein was confirmed by immunohistochemistry. Hence, the kidney lesions were attributed to sex- and species-specific α-2u-globulin nephropathy and not considered to be a human health concern. Increases in absolute and liver weights were accompanied by minimal centrilobular hypertrophy which was completely reversed in females and partially in males during the recovery period. Thus, the liver lesions were not considered to be treatment-related adverse effects. All reported hematological and clinical chemistry changes in the high-dose group were reversed during the recovery period with the exception of increased levels of cholesterol in male rats. Since this alteration was not observed in

Table 1
Summary of 28-day OECD TG 407 dietary study.

Duration	Animals/Sex/Dose	Route	Compliance	Doses	Adverse effects	NOAEL	Ref
28 days	5 SD rats/sex/dose	Oral (diet)	OECD TG 407 and GLP	0, 545, 5455, 10910 ppm (**Males:** 0, 44, 436, 881 mg/kg/day; **females:** 0, 51, 482, 953 mg/kg/day, respectively)	None	44 mg/kg/day	RIFM, 2000e

female animals during recovery, it was not considered a treatment-related adverse effect. Based on persistent bodyweight gain reduction in both sexes after a 5-week recovery period, the 5000 ppm dose was considered to be the NOAEL for repeated dose toxicity. As reported in the study, the 5000 ppm dose is equivalent to 287 and 351 mg/kg/day in males and females, respectively. An additional study of shorter duration is summarized in Table 1 below (conducted according to OECD TG 407). Since the OECD TG 408 study was for a longer treatment and recovery duration in comparison to the OECD TG 407 study, the NOAEL for this risk assessment is derived from the 90-day study. **The lowest available NOAEL of 287 mg/kg/day was considered for repeated dose toxicity endpoint (ECHA, 2013).**

Therefore, the acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester MOE can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure to be, 287/0.031 or 9258.

Additional References: RIFM, 2000a; RIFM, 2008b; Belsito et al., 2008; RIFM, 2008a.

Literature Search and Risk Assessment Completed On: 10/22/15.

10.1.3. Reproductive toxicity

The MOE for acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (Romandolide) that can be used to support the reproductive toxicity endpoint. An OECD 421/GLP dietary reproduction/developmental toxicity screening test was conducted in Crl:CD(SD) rats. Groups of 10 rats/sex/dose were fed diets containing Romandolide at concentrations of 0, 500, 5000, or 11000 ppm (equivalent to doses of 0, 31, 309, and 698 mg/kg/day for males and 0, 37–70, 370–722, and 737–1467 mg/kg/day for females). The control and 11000 ppm groups also included 5 toxicity-phase females that were not mated and were maintained for the purposes of assessing systemic toxicity in non-pregnant females. The males and toxicity-phase females were treated for at least 6 weeks. The main-phase females were treated for 2 weeks before mating, throughout mating, gestation, and until day 6 of lactation. No effects were reported for mortality, clinical signs of toxicity, body weight, or food consumption in any of the treated rats. Estrous cycle length, mating performance, fertility, reproductive capacity, and gestation length were not affected by treatment. With the exception of 1 non-pregnant main-phase female receiving the 500 ppm diet, all main-phase females became pregnant, successfully gave birth, and reared the F1 pups to scheduled termination on day 7 after birth. Survival, bodyweight gain, and development of the pups to day 7 were not affected by parental treatment. No treatment-related macroscopic or microscopic abnormalities were observed in the reproductive organs of parental animals during necropsy. The NOAEL for effects on fertility and on the development of pups was considered to be 11000 ppm, the highest dose tested (ECHA, 2013).

The most conservative NOAEL of 698 mg/kg/day from males was selected for the fertility endpoint. **Therefore, the acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester MOE 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 to acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester, 698/0.031 or 22516.**

The most conservative NOAEL of 737 mg/kg/day from females was selected for the developmental toxicity endpoint. **Therefore, the acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester MOE 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 to acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester, 737/0.031 or 23774.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/19.

10.1.4. Skin sensitization

Based on the existing data and read-across material *d*-cyclocitronellene acetate (CAS # 25225-10-9), acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl) ethyl ester. Based on the available data and read-across analog *d*-cyclocitronellene acetate (CAS # 25225-10-9; see Section V), acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not present a concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In guinea pigs, maximization tests with acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl) ethyl ester and the read-across material did not present reactions indicative of sensitization (RIFM, 1999d; RIFM, 1981). In a human maximization test, no skin sensitization reactions were observed with read-across material *d*-cyclocitronellene acetate (RIFM, 1982). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 59055 μg/cm^2 of acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester, no reactions indicative of sensitization was observed in any of the 12 volunteers (RIFM, 2011). In multiple HRIPTs with read-across material *d*-cyclocitronellene acetate, no reactions indicative of sensitization were observed in any of the volunteers (RIFM, 1977a; RIFM, 1977b; RIFM, 1977c; RIFM, 1977d).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and data on read-across material *d*-cyclocitronellene acetate, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/15/19.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester 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 acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/06/19.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester 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 acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester. Based on the Creme RIFM Model, the inhalation exposure is 0.20 mg/day. This exposure is 7.0 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: 06/21/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US ECHA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester 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 EPI Suite v4.11 (US EPA, 2012a) did not identify acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥ 2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence 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 VoU (IFRA, 2015), acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2000b: Biodegradation of the test material was measured using the carbon dioxide evolution test method according to OECD 301B guidelines. Biodegradation of 37% was observed after 28 days.

RIFM, 2000i: Biodegradation of the test material was evaluated in a closed bottle test according to OECD 301D guidelines. Under the conditions of the study, biodegradation of 68% was observed.

10.2.3.2. Ecotoxicity. RIFM, 2000f: An algae inhibition test was conducted according to OECD 201 guidelines under static conditions. Under the conditions of the study, the 96-hour EbC50 and ErC50 were greater than 3.73 mg/L (based on measured concentrations).

RIFM, 2000g: A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 method under semi-static conditions. Under the conditions of the study, the 48-hour EC50 was reported to be greater than 3.16 mg/L.

RIFM, 2000h: A fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. Under the conditions of the study, the 96-hour LC50 was reported to be 1.26 mg/L.

10.2.4. Other available data

Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester has been registered under REACH with the following additional data:

A fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. Under the conditions of the study, the 96-hour LC50 was reported to be 1.6 mg/L (95% CI: 1.3–1.8 mg/L) (ECHA, 2013).

10.2.5. Risk assessment refinement

Since acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester has passed the screening criteria (Tier 2), measured data has been included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	(Fish) (mg/L)	(*Daphnia*) (mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	1.363			1,000,000	0.001363	
ECOSAR Acute Endpoints **(Tier 2) *v1.11***	1.333	2.131	0.615	10,000	0.0615	Esters
ECOSAR Acute Endpoints **(Tier 2) *v1.11***	1.388	0.989	1.888			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.7	4.7
Biodegradation Factor Used	1	1
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 further assessment is necessary.

The RIFM PNEC is 0.0615 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/30/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/01/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111342.

Appendix

Read-across Justification

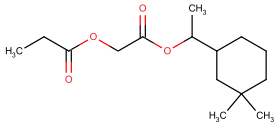
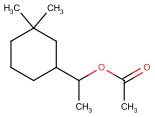
Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were

examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.

- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester	*d*-Cyclocitronellene acetate
CAS No.	236391-76-7	25225-10-9
Structure		
Similarity (Tanimoto Score)		0.69
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{15}H_{26}O_4$	$C_{12}H_{22}O_2$
Molecular Weight	270.36	198.30
Melting Point (°C, EPI Suite)	5.19	13.46
Boiling Point (°C, EPI Suite)	294.03	230.13
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.57E-01	1.04E + 01
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.45	4.42
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2.856	7.462
J_{max} (μg/cm^2/h, SAM)	1.594	13.387
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.25E + 00	1.00E + 02
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• 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)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Acyl Transfer agent identified	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, read-across material *d*-cyclocitronellene acetate (CAS # 25225-10-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- *d*-Cyclocitronellene acetate (CAS # 25225-10-9) was used as a read-across analog for the target material acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester (CAS # 236391-76-7) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of esters.
  - o The target material and the read-across analog share a cyclic secondary alcohol containing an ester functional group.
  - o The key difference between the target material and the read-across analog is that the target material is a diester while the read-across analog is a monoester. The target material and the read-across analog are both expected to produce very similar secondary alcohols. These structural differences are toxicologically insignificant for the skin sensitization endpoint.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. This makes the choice of the read-across analog more conservative. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

- o The target material has an alert for an acyl transfer agent for skin sensitization. The data described in the skin sensitization section above confirm that based on the existing data on the target material and the data for read-across material, the target material does not present a concern for skin sensitization under the current, declared levels of use. The predictions are superseded by data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between 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.

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, and 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? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? Yes
Q18. One of the list? (see Cramer et al., 1978 for detailed explanation on list of categories) No Class I (Class Low)

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