Food and Chemical Toxicology 156 (2021) 112537

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one, CAS Registry Number 84642-57-9

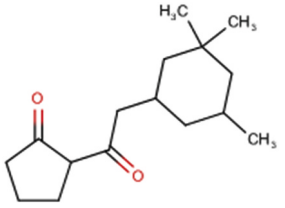
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 112020. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



(*continued on next column*)

(*continued*)

Name: 2-[(3,3,5-Trimethylcyclohexyl) acetyl]cyclopentan-1-one CAS Registry Number: 84642-57-9

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

(*continued on next page*)

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2021.112537
Received 15 April 2021; Received in revised form 30 July 2021; Accepted 29 August 2021
Available online 4 September 2021

(*continued*)

CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
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, 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.

2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one is not genotoxic and provided a No Expected Sensitization Induction Level (NESIL) of 1500 μg/cm^2 for the skin sensitization endpoint. The repeated dose, reproductive (developmental toxicity and fertility), and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on data; 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1981a; RIFM, 2014)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 1500 μg/cm^2.	RIFM (2015a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(RIFM, 1983a; RIFM, 1983b; RIFM, 1983c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 0% (OECD 302C)	RIFM (2002a)
Bioaccumulation:	
Screening-level: 258.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 1.24 mg/L	(RIFM Framework; Salvito et al., 2002)
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: LC50: 1.24 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00124 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one
2. **CAS Registry Number:** 84642-57-9
3. **Synonyms:** Cyclopentanone, 2-[(3,3,5-trimethylcyclohexyl)acetyl]-; Dione; 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one
4. **Molecular Formula:** $C_{16}H_{26}O_2$
5. **Molecular Weight:** 250.38
6. **RIFM Number:** 6016
7. **Stereochemistry:** Isomer not specified. Three chiral centers and 8 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 331.07 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.8 (RIFM, 2002b), 4.16 (EPI Suite)
4. **Melting Point**: 96.4 °C (EPI Suite)
5. **Water Solubility:** 6.428 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 7.5e-005 mm Hg at 25 °C (EPI Suite), 0.0000378 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Absorbs between 290 and 700 nm, with peak at 290 nm and returning to baseline by 340 nm; molar absorption coefficient is above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient

1. **95**th **Percentile Concentration in Fine Fragrance**: 0.043% (RIFM, 2019)
2. **Inhalation Exposure***: 0.000060 mg/kg/day or 0.0046 mg/day (RIFM, 2019)
3. **Total Systemic Exposure****: 0.00045 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate* (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	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 Appendix below for further details.

2. **Analogs Selected**:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity**: None
   c. **Reproductive Toxicity**: None
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional references

None.

8. Natural occurrence

2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one 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.

9. REACH dossier

No dossier available as of 09/29/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.12
2	Products applied to the axillae	0.034
3	Products applied to the face/body using fingertips	0.69
4	Products related to fine fragrances	0.64
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.16
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.16
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.16
5D	Baby cream, oil, talc	0.16
6	Products with oral and lip exposure	0.38
7	Products applied to the hair with some hand contact	1.3
8	Products with significant ano-genital exposure (tampon)	0.068
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.3
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.5
10B	Aerosol air freshener	4.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	2.5
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one, the basis was a skin sensitization NESIL of 1500 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-[(3,3,5-Trimethylcyclohexyl) acetyl]cyclopentan-1-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic

activation, negative for genotoxicity without metabolic activation, and positive for both cytotoxicity and genotoxicity with metabolic activation (RIFM, 2015b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2-[(3,3,5-trimethylcyclohexyl)acetyl] cyclopentan-1-one was assessed in an Ames study conducted in compliance with GLP regulations. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one in DMSO (dimethyl sulfoxide) at the concentrations of 0.0016, 0.0031, 0.0063, 0.0125, 0.025, 0.05, and 0.10 μl/plate in the presence and absence of metabolic activation. No significant increase in the frequency of revertant colonies was detected in the strains at the test concentrations (RIFM, 1981a). Under the conditions of the study, 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one was considered not mutagenic in bacteria.

The clastogenicity of 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one was assessed in an in vitro micronucleus study conducted in compliance with GLP regulations in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one in DMSO at concentrations up to 2500 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. The percentage of cells with micronucleated binucleated cells in the test substance-treated groups was not statistically significantly increased relative to vehicle control at any concentration (RIFM, 2014). Under the conditions of the study, 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one was considered negative for clastogenicity in mammalian cells.

Based on the available data, 2-[(3,3,5-trimethylcyclohexyl)acetyl] cyclopentan-1-one does not present a concern for genotoxic potential.

Additional references

None.

Literature Search and Risk Assessment Completed On

11/03/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one or any read-across materials. The total systemic exposure to 2-[(3,3,5-trimethylcyclohexyl)acetyl] cyclopentan-1-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-[(3,3,5-trimethylcyclohexyl) acetyl]cyclopentan-1-one (0.45 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional references

None.

Literature Search and Risk Assessment Completed On

10/06/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one or any read-across materials. The total systemic exposure to 2-[(3,3,5-trimethylcyclohexyl)acetyl] cyclopentan-1-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one or any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure to 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one (0.45 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional references

None.

Literature Search and Risk Assessment Completed On

10/31/20.

11.1.4. Skin sensitization

Based on the available data, 2-[(3,3,5-trimethylcyclohexyl)acetyl] cyclopentan-1-one is considered a skin sensitizer with a defined NESIL of 1500 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data, 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD toolbox v4.2). In an Open Epicutaneous Test and Freund's Complete Adjuvant Test in guinea pigs, 2-[(3,3,5-trimethylcyclohexyl) acetyl]cyclopentan-1-one has been reported to be a skin sensitizer (RIFM, 1981b). In 2 Confirmation of No Induction in Humans tests (CNIH) with 51 subjects each, equivocal results for skin sensitization were reported (RIFM, 1982a; RIFM, 1982b). In another CNIH with 1.3% (1535 μg/cm2) 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one in 1:3 ethanol:DEP, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2015a).

Based on the weight of evidence (WoE) from structural analysis, animal data, and human studies, 2-[(3,3,5-trimethylcyclohexyl)acetyl] cyclopentan-1-one is considered to be a skin sensitizer with a defined NESIL of 1500 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020).

Additional references

None.

Literature Search and Risk Assessment Completed On

11/02/20.

11.1.5. Phototoxicity/photoallergenicity

Based on existing data 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis spectra were obtained and indicate absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline at 340 nm. The molar absorption coefficient is

Table 1
Data summary for 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one.

LLNA EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3] μg/cm^2
NA	NA	1535	NA	NA	1500

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[2] Data derived from CNIH or HMT.

[3] WoE NESIL limited to 2 significant figures.

above the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Phototoxicity and photoallergenicity of 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one were evaluated *in vivo* in guinea pigs, and there were no reactions when the material was applied alone, without the addition of a UV-absorber (RIFM, 1983a; RIFM, 1983c). In a human phototoxicity study, 3% 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one in an ethanol/acetone (1:1) vehicle did not result in phototoxic reactions in 6 female volunteers (RIFM, 1983b). Based on the *in vivo* studies, 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis spectra were obtained and indicate absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline at 340 nm. The molar absorption coefficient is above the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009).

Additional references

None.

Literature Search and Risk Assessment Completed On

11/03/20.

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level for 2-[(3,3,5-trimethylcyclohexyl) acetyl]cyclopentan-1-one is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0046 mg/day. This exposure is 102.2 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional references

None.

Literature Search and Risk Assessment Completed On

11/05/20.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-[(3,3,5-trimethylcyclohexyl) acetyl]cyclopentan-1-one was performed following the RIFM Environmental Framework (Salvito, 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 EPA, 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, 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one was identified as a fragrance material with no 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) identified 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one as possibly persistent but not 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, 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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-[(3,3,5-trimethylcyclohexyl)acetyl]cyclopentan-1-one does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2002a:** The inherent biodegradability of the test material was evaluated by the Manometric respirometry test according to the OECD 302 C guideline. No biodegradation was observed after 35 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2-[(3,3,5-Trimethylcyclohexyl) acetyl]cyclopentan-1-one has been pre-registered for REACH with no additional data at this time.

11.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. Further assessment is necessary.

The RIFM PNEC is 0.00124 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 VoU.

Literature Search and Risk Assessment Completed On: 11/06/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.24			1,000,000	0.00124	

- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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 05/15/20.

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.2021.112537.

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., Renskers, 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.

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.

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.

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.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment, November 2012 v2.1. http://echa.europa.eu/.

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, 2015. Volume of Use Survey, February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance Skin Sensitization Evaluation and Human Testing, Dermatitis: November 16, 2020. Volume Publish Ahead of Print Issue. https://doi.org/10.1097/DER.0000000000000684.

RIFM Research Institute for Fragrance Materials, Inc, 1981a. Mutagenicity Evaluation of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione) in the Ames Salmonella/Microsome Plate Test. Unpublished Report from Givaudan. RIFM Report Number 56232. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1981b. 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one (Dione): Skin Irritation and Capacity of Allergenic Sensitization Determined by the Open Epicutaneous Test (OET) on guinea Pigs. Unpublished Report from Givaudan. RIFM Report Number 56239. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1982a. Clinical Safety Evaluation of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione): Repeated Insult Patch Test. Unpublished Report from Givaudan. RIFM Report Number 56237. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1982b. Repeat Insult Patch Test with 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione). Unpublished Report from Givaudan. RIFM Report Number 56238. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1983a. Determination of Phototoxicity of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione) in guinea Pigs. Unpublished Report from Givaudan. RIFM Report Number 56233. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1983b. 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one (Dione): A Phototoxicity Test in Humans. Unpublished Report from Givaudan. RIFM Report Number 56234. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1983c. Determination of Photoallergenicity of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione) in guinea Pigs. Unpublished Report from Givaudan. RIFM Report Number 56235. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2002a. Inherent Biodegradability of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione). Unpublished Report from Givaudan. RIFM Report Number 56229. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2002b. Partition Coefficient N-Octanol/water of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One (Dione).

Unpublished Report from Givaudan. RIFM Report Number 56236. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2014. 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM Report Number 67680. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015a. 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-one: Repeated Insult Patch Test. RIFM Report Number 68613. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015b. Report on the Testing of 2-[(3,3,5-Trimethylcyclohexyl)acetyl]cyclopentan-1-One in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 69494. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.
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.
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.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.