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RIFM fragrance ingredient safety assessment, 6,6-dimethylbicyclo[3.1.1] hept-2-ene-2-propionaldehyde, CAS Registry Number 33885-51-7

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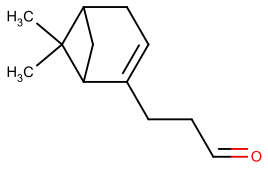
Name: 6,6-Dimethylbicyclo[3.1.1] hept-2-ene-2-propionaldehyde
CAS Registry Number: 33885-51-7



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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BCF - Bioconcentration Factor
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., 2015a, 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 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
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.

6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-52-8) provided 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde a No Expected Sensitization Induction Level (NESIL) of 4700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is below the TTC for local respiratory effects (0.47 mg/day). The environmental endpoints were evaluated; 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde 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.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2016; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 40 mg/kg/day.	RIFM, (2020d)
Reproductive Toxicity: Developmental NOAEL = 60 mg/kg/day. Fertility NOAEL = 60 mg/kg/day.	RIFM, (2020d)
Skin Sensitization: NESIL = 4700 μg/cm^2.	RIFM, (2018)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC is not available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 72% (OECD 301D)	(ECHA REACH Dossier: 6,6-Dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde; ECHA, 2017a)
Bioaccumulation: Screening-level: 140 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.817 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, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.817 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0817 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

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1. Identification

1. **Chemical Name:** 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde
2. **CAS Registry Number:** 33885-51-7
3. **Synonyms:** Bicyclo[3.1.1]hept-2-ene-2-propanal, 6,6-dimethyl-; 6,6-Dimethyl 2-norpinene-2-propionaldehyde; 3-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)propanal; Pino Acetaldehyde; Pino acetald; 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde
4. **Molecular Formula:** $C_{12}H_{18}O$
5. **Molecular Weight:** 178.27
6. **RIFM Number:** 5664
7. **Stereochemistry:** Isomer not specified. Two chiral centers and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 246.66 °C (EPI Suite)
2. **Flash Point:** 89 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.76 (EPI Suite)

4. **Melting Point**: 44.75 °C (EPI Suite)
5. **Water Solubility:** 34.44 mg/L (EPI Suite)
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.012 mm Hg at 20 °C (EPI Suite v4.0), 0.0209 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol• cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.053% (RIFM, 2020a)
2. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0083 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.00098 mg/kg/day (RIFM, 2020a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2017; Safford, 2015, 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	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-52-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde 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

Available (ECHA, 2017a); accessed 07/16/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.23
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	0.15
4	Products related to fine fragrances	2.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.51
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.076
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.15
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	0.68
7	Products applied to the hair with some hand contact	0.15
8	Products with significant ano-genital exposure (tampon)	0.025
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.46
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.23
10B	Aerosol air freshener	1.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.025
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	94

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 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde, the basis was the reference dose of 0.40 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 4700 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). 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 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and 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 6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde in solvent 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, 2016). Under the conditions of the study, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde was not mutagenic in the Ames test.

The clastogenic activity of 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde in DMSO at concentrations up to 1783 μg/mL for the dose range finding (DRF) study. Micronuclei analysis was conducted at concentrations ranging up to 120 μg/mL (based on cytotoxicity) in the presence and absence of metabolic activation (S9) for 4 h and the absence of metabolic activation for 24 h 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, 6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test.

Additional References: RIFM, 2020c.

Literature Search and Risk Assessment Completed On: 06/09/21.

11.1.2. Repeated dose toxicity

The MOE for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde. In a GLP and OECD 422-compliant study, 10 Wistar Han rats/sex/dose were administered 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde via gavage at doses of 0, 30, 60, and 120 mg/kg/day for a minimum of 28 days. Doses were selected based on a DRF study in which mortality was observed at 450 mg/kg/day, but no severe effects were observed at 90 mg/kg/day. No treatment-related mortality was seen up to the highest dose. No treatment-related effects were observed in clinical appearance, functional observations, body weight, food consumption, hematology, clotting parameters, hormone levels. Total serum protein concentrations were reduced in males at the mid and high doses, but this effect was not considered adverse due to a lack of correlated gross or histopathological findings. Liver weight and periportal hepatocellular hypertrophy incidence were significantly increased in females at the mid dose and in both sexes at the high dose; however, these effects were slight and were not accompanied by any degenerative findings. Thus, liver effects were not considered adverse. Based on no treatment-related adverse effects seen up to the highest dose, the NOAEL for this study was considered to be 120 mg/kg/day (RIFM, 2020d).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 120/3 or 40 mg/kg/day.

Therefore, the 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure to 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde, 40/0.00098 or 40816.

In addition, the total systemic exposure to 6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde (0.98 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

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, 2020b) and a reference dose (RfD) of 0.40 mg/kg/day.

11.1.3. Derivation of RfD

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for 6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 40 mg/kg/day by the uncertainty factor, 100 = 0.40 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.4. Reproductive toxicity

The MOE for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.4.1. Risk assessment. There are sufficient reproductive toxicity data on 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde. In a GLP and OECD 422-compliant study, 10 Wistar Han rats/sex/dose were administered 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde via gavage at doses of 0, 30, 60, and 120 mg/kg/day for a minimum of 28 days. Doses were selected based on a DRF study in which significant treatment-related changes in sperm parameters (reduced mean motile sperm, mean progressive motility, the mean number of cells with normal morphology, the mean number of cells with coiled tail, increased mean number of cells with detached head, and mean number of cells with abnormal neck) were observed at 450 mg/kg/day, but none of these effects were observed at 90 mg/kg/day. Sperm analyses were not as extensive in the main study, so it is possible that the previously mentioned sperm effects seen in the DRF study also occurred at the high dose (120 mg/kg/day) of the main study. In the main study, the fertility index was adversely affected (reduced to 50%) at the high dose, which may be related to undetected sperm effects. No treatment-related effects were observed in the mating index, precoital time, number of

implantations, estrous cycle, spermatogenic profiling, or histopathological examination of reproductive organs. Based on decreased fertility index at 120 mg/kg/day, the fertility NOAEL for this study was considered to be 60 mg/kg/day (RIFM, 2020d).

Therefore, the 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde MOE for the reproductive toxicity endpoint can be calculated by dividing the 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure to 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde, 60/0.00098 or 61224.

In addition, the total systemic exposure to 6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde (0.98 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.5. Skin sensitization

Based on the existing data and read-across material α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-52-8), 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is considered a skin sensitizer with a defined NESIL of 4700 μg/cm^2.

11.1.5.1. Risk assessment. Limited skin sensitization studies are available for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde. Based on the existing data and read-across material α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-52-8; see Section VI), 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is considered a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In murine local lymph node assays (LLNAs), 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde and read-across material α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde were found to be sensitizing with EC3 values of 25% (6250 μg/cm^2) and 19.2% (4800 μg/cm^2), respectively (ECHA, 2017a; RIFM, 2010b; ECHA, 2018; RIFM, 2010a). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2.5% (1937 μg/cm^2) of 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2--propionaldehyde, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1972). Similarly, in 2 other CNIHs with read-across material α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde at 2.5% (1938 μg/cm^2) in alcohol SDA 39 and 4% (4724 μg/cm^2) in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 41 and 104 volunteers, respectively (RIFM, 1971; RIFM, 2018).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data on the read-across material α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is a sensitizer with a WoE NESIL of 4700 μg/cm^2 (see 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, 2020b) and a reference dose of 0.40 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.6. Phototoxicity/photoallergenicity

Based on available UV spectra, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. There are no phototoxicity studies available for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. As such, it is not a concern for phototoxicity or photoallergenicity (Henry, 2009). Based on the lack of absorbance, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde does not present a concern for phototoxicity or photoallergenicity.

Table 1
Data summary for α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde as read-across material for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
4800 (1)	Weak	4724	NA	NA	4700

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.

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.7. UV spectra analysis

The available spectra indicate no absorbance in the range of 290–400 nm. As the material does not absorb in the range of interest, it is not a concern for phototoxicity or photoallergenicity (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.8. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.8.1. Risk assessment. There are no inhalation data available on 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.0083 mg/day. This exposure is 56.6 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 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: 06/24/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde 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, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde 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 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde as possibly 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, 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.

11.2.1.1. Risk assessment. Based on the current VoU (2015), 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

Biodegradation: No data available.

Ecotoxicity: No data available.

11.2.2.1. Other available data. 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde has been registered under REACH and the following additional data is available (ECHA, 2017a):

A ready biodegradability study was conducted according to the OECD 301 D method, and biodegradation of 14% was observed after 28 days. In the prolonged closed bottle test, biodegradation was 72% at 60 days.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions and the 48-h EC50 based on measured concentration was reported to be 0.67 mg/L.

An algae inhibition study was conducted according to the OECD 201 method under static conditions and the 72-h EC50 (growth rate) based on mean measured concentration was reported to be 4.2 mg/L.

11.2.2.2. Risk assessment refinement. Since 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde has passed the screening criteria, measured data are included for completeness and have 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.

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

Exposure	Europe	North America
Log K_{ow} Used	3.76	3.76
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.0817 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: 06/25/21.

12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	7.077			1000000	0.007077	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.219	0.817	1.858	10000	0.0817	Aldehydes (mono)

- **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 07/16/21.

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.2021.112658.

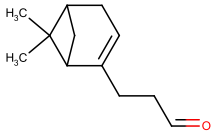
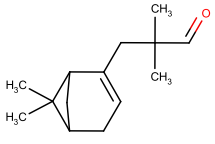
Appendix

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, 2017b).

- 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	6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde	α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde
CAS No.	33885-51-7	33885-52-8
Structure		
Similarity (Tanimoto Score)		0.98
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_{12}H_{18}O$	$C_{14}H_{22}O$
Molecular Weight	178.27	206.32
Melting Point (°C, EPI Suite)	44.75	54.98
Boiling Point (°C, EPI Suite)	246.66	263.89
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.78	0.915

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.76	4.63
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	34.44	4.492
J_{max} (μg/cm^2/h, SAM)	32.30	9.48
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.36E+001	4.16E+001
Skin Sensitization		
Protein Binding (OASIS v1.1)	• Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Protein Binding (OECD)	• Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
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)	• Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Schiff base formation	Alert for Schiff base formation
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 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-51-7). 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, α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-52-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-52-8) was used as a read-across analog for the target material 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33885-51-7) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of cycled bridged unsaturated aldehydes.
  - o The target material and the read-across analog share a bicyclic bridged unsaturated aldehyde structure.
  - o The key structural difference between the target material and the read-across analog is that the target material has a propionaldehyde moiety, while the read-across analog has a dimethyl propionaldehyde moiety. This structural difference is toxicologically insignificant.
  - 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 ≤80% and J_{max} for the read-across analog corresponds to skin absorption ≤40%. 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 and the read-across analog have alerts for Schiff base formation. This is due to an aldehyde group present in both. The data described in the skin sensitization section confirm that the material is a skin sensitizer. *In silico* alerts are consistent with data. 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.

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