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RIFM fragrance ingredient safety assessment, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde, CAS Registry Number 67845-30-1

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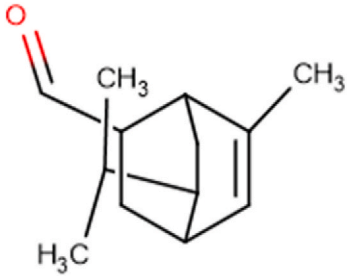

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Name: 8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde
CAS Registry Number: 67,845-30-1

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

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(*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., 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 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.

8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data from read-across analog α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8) provided 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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 data and ultraviolet/visible (UV/Vis) spectra; 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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, 1982d; RIFM, 1988)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 4700 μg/cm^2. RIFM (2018)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1982b; RIFM, 1982c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 0% (OECD 301 B) (RIFM, 1996)
Bioaccumulation:
Screening-level: 251.5 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 3.57 mg/L (RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 3.57 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.00357 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde
2. **CAS Registry Number:** 67,845-30-1
3. **Synonyms:** Bicyclo [2.2.2]oct-5-ene-2-carboxaldehyde, 6-methyl-8-(1-methylethyl)-; 2-Methyl-5-(1-methylethyl)bicyclo [2.2.2]oct-2-ene-7-carboxaldehyde; Maceal; 8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde
4. **Molecular Formula:** $C_{13}H_{20}O$
5. **Molecular Weight:** 192.3
6. **RIFM Number:** 5860
7. **Stereochemistry:** Stereoisomer not specified. Two chiral centers present and 1 geometric center present. A total of 16 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 259.26 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.14 (EPI Suite)
4. **Melting Point**: 30.74 °C (EPI Suite)
5. **Water Solubility:** 13.86 mg/L (EPI Suite)

(*continued on next column*)

6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00837 mm Hg at 20 °C (EPI Suite v4.0), 0.0147 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00046% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000011 mg/kg/day or 0.00081 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.000032 mg/kg/day (RIFM, 2019)

*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)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	III	I

*See the Appendix below for details.

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 # 33,885-52-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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

Pre-registered for 2010; no dossier available as of 09/22/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.36
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	2.2
4	Products related to fine fragrances	2.0
5 A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.51
5 B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.51
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.51
5D	Baby cream, oil, talc	0.51
6	Products with oral and lip exposure	1.2
7	Products applied to the hair with some hand contact	4.1
8	Products with significant ano-genital exposure (tampon)	0.21
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.9
10 A	Household care products with mostly hand contact (hand dishwashing detergent)	14
10 B	Aerosol air freshener	14
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	7.8
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 8-isopropyl-6-methylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde, the basis was 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde has been evaluated in

a bacterial reverse mutation assay conducted in compliance with GLP regulations and OECD TG 471 guidelines using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde in ethanol at concentrations up to 50,000 μg/plate. Non-dose-responsive increases in revertant colonies were observed in TA100 in the presence and absence of S9, however, these increases were not reproducible in 2 additional experiments and were considered not biologically relevant. No increases in the mean number of revertant colonies were observed at any other tested concentration and strain in the presence or absence of S9 (RIFM, 1982d). Under the conditions of the study, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde was not mutagenic in the Ames test.

The clastogenicity of 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde in dimethyl sulfoxide for 6 h 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, 1988). Under the conditions of the study, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde was considered to be non-clastogenic to mammalian cells.

Based on the data available, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde or any read-across materials. The total systemic exposure to 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde (0.032 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.

Additional References: None.

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

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde or any read-across materials. The total systemic exposure to 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde (0.032 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.

11.1.4. 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 # 33,885-52-8), 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde is considered a skin sensitizer with a defined NESIL of 4700 μg/cm^2.

11.1.4.1. Risk assessment. 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 a murine local lymph node assay (LLNA), read-across material α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde was found to be sensitizing with an EC3 value of 19.2% (4800 μg/cm^2) (RIFM, 2010). In a guinea pig maximization test, the target material 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde did not present reactions indicative of sensitization at 100% (RIFM, 1982a). In 2 Confirmation of No Induction Humans tests (CNIHs), read-across material α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde did not present reactions indicative of sensitization when tested at 2.5% (1938 μg/cm^2) in alcohol SDA 39C or at 4% (4724 μg/cm^2) in 1:3 ethanol:diethyl phthalate in any of the 41 and 104 volunteers, respectively (RIFM, 1971; RIFM, 2018).

Based on the available data on read-across material α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde, summarized in Table 1, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 4700 μg/cm^2. **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: 06/24/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the UV/Vis absorption spectra and available *in vivo* study data, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde in

Table 1
Data Summary for α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde as read-across material for 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde.

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.

experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In studies conducted in guinea pigs, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde did not show evidence of phototoxicity or photoallergenicity (RIFM, 1982b; RIFM, 1982c). Based on the *in vivo* study data and the lack of absorbance, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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} • cm^{-1} (Henry, 2009).

Additional References: None.

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

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.00081 mg/day. This exposure is 580.2 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 8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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, 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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), 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1996:** The biodegradability of the test material was evaluated according to the OECD 301 B method. Under the conditions of this study, no biodegradation was observed after 28 days.

RIFM, 1993: The biodegradability of the test material was evaluated according to the OECD 301 B method. Under the conditions of this study, no biodegradation was observed after 56 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde 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, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.14	4.14
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. No further assessment is necessary.

The RIFM PNEC is 0.00357 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.57			1000000	0.00357	

- **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 09/22/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112677.

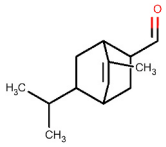
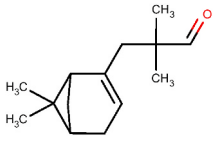
Appendix

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 Chemical Agency read-across assessment framework (ECHA, 2017).

- 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	8-Isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde	α,α,6,6-Tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde
CAS No.	67,845-30-1	33,885-52-8
Structure		
Similarity (Tanimoto Score)		0.91
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{13}H_{20}O$	$C_{14}H_{22}O$
Molecular Weight	192.30	206.32
Melting Point (°C, EPI Suite)	30.74	54.98
Boiling Point (°C, EPI Suite)	259.26	263.89
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.96	0.915
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.14	4.63
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	13.86	4.492
J_{max} (μg/cm^2/h, SAM)	39.63	9.48
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.13 E+001	4.16 E+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 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde (CAS # 67,845-30-1). 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 # 33,885-52-8) 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 # 33,885-52-8) was used as a read-across analog for the target material 8-isopropyl-6-methylbicyclo [2.2.2]oct-5-ene-2-carbaldehyde (CAS # 67,845-30-1) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of alkyl aldehydes containing an unsaturated bridged macrocycle.
  - o The target material and the read-across analog share an alkyl aldehyde group with a bridged unsaturated bicyclic ring substituent.
  - o The key difference between the target material and the read-across analog is that whereas the target material has an alkyl aldehyde group attached to a bridged bicyclic ring, the read-across analog has a 2,2-dimethyl propanal attached to a bridged bicyclic ring. The unsaturation in the target material is in the bridge, whereas the read-across analog has a cyclohexene ring. The target material has an isopropyl branch, whereas the read-across analog has a dimethyl substitution. These structural differences are 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 $\leq$80% and J_{max} for the read-across analog corresponds to skin absorption $\leq$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 Both the target material and the read-across analog display several alerts related to the aldehyde group. Data are consistent with *in silico* alerts.
- 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
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? NO
Q26. Monocycloalkanone or a bicyclo compound? Yes, Class II (Class moderate)

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