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RIFM fragrance ingredient safety assessment, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde, CAS Registry Number 472-66-2

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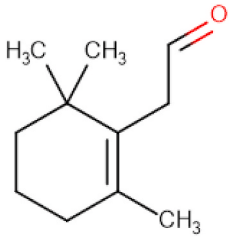
CAS Registry Number: 472-66-2



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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
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., 2021)
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.,

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2015, 2017; Safford et al., 2015a; Safford et al., 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 et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde 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 I material, and the exposure to 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from the target material and read-across analog 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7) provided a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2015a; RIFM, 2015b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 1100 μg/cm^2. RIFM (2009)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.64 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 181.4 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 4.695 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: Fish LC50: 4.695 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.004695 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde
2. **CAS Registry Number:** 472-66-2
3. **Synonyms:** 1-Cyclohexen-1-acetaldehyde, 2,6,6-trimethyl-; β-Homocyclocitral; (2,6,6-Trimethylcyclohex-1-en-1-yl)acetaldehyde; 2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde
4. **Molecular Formula:** $C_{11}H_{18}O$
5. **Molecular Weight:** 166.26
6. **RIFM Number:** 6137
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 58 °C at 0.4 mm Hg (Fragrance Materials Association [FMA]), 232.55 °C (EPI Suite)
2. **Flash Point:** 164 °F; CC (FMA)
3. **Log K_{OW}:** 3.93 (EPI Suite)
4. **Melting Point:** 30.89 °C (EPI Suite)
5. **Water Solubility:** 28.31 mg/L (EPI Suite)
6. **Specific Gravity:** 0.941 (FMA)
7. **Vapor Pressure:** 0.0338 mm Hg at 20 °C (EPI Suite v4.0), 0.04 mm Hg at 20 °C (FMA), 0.0574 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 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00010% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0000049 mg/kg/day or 0.00032 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.000020 mg/kg/day (RIFM, 2018)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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 et al., 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 I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 4-(2,6,6-Trimethyl-2-cyclohexen)-2-methyl-butanal (CAS # 65405-84-7)
   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.

7.1. Additional References

None.

8. Natural occurrence

2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde is reported to occur in the following foods by the VCF*:

Brown algae.

Mangifera species.

Rice (*Oryza sativa* L.)

*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

2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde has been pre-registered for 2010; no dossier available as of 12/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.085
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.51
4	Products related to fine fragrances	0.47
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.12
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.12
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.96
8	Products with significant ano-genital exposure (tampon)	0.050
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.92
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.3
10B	Aerosol air freshener	3.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.8
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde, the basis was a skin sensitization NESIL of 1100 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; December 2019).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The material, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde, was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). 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 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde was not mutagenic in the Ames test.

The clastogenic activity of 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde in DMSO at concentrations up to 500 μg/mL in the presence and absence of S9 for 3 and 24 h. The material, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde, did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015b). Under the conditions of the study, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde or any read-across materials. The total systemic exposure to 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde (0.020 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/30/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde or any read-across materials. The total systemic exposure to 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde (0.020 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/30/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7), 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is a skin sensitizer with a defined NESIL of 1100 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde. Based on the existing data and read-across to 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7; see Section VI), 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal, was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (RIFM, 2015c; ECHA, 2017b). No animal studies are available for 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde. However, in a murine local lymph node assay (LLNA), read-across 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal was found to be positive with an EC3 value of 20.6% (5150 μg/cm^2) (ECHA, 2011). Similarly, in a guinea pig open epicutaneous test, read-across 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal was found to be a weak sensitizer (RIFM, 1981a). In a human maximization test, no skin sensitization reactions were observed with 10% or 6900 μg/cm^2 read-across 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal in petrolatum (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH), no reactions indicative of sensitization were observed in any of the 102 and 107 volunteers, respectively, tested with 1% or 551 μg/cm^2 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde (RIFM, 2013b) or 1% or 1181 μg/cm^2 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal in 3:1 diethyl phthalate:ethanol (RIFM, 2009).

Based on the existing data and read-across to 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is considered a skin sensitizer with a defined NESIL of 1100 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).

Additional References: RIFM, 1978; RIFM, 1981b.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Data summary for 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal.

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
5150 [1]	weak	1181	6897	NA	1100

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.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde in 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 et al., 2009). Based on the lack of absorbance, 2,6,6-trimethyl-1--cyclohexen-1-acetaldehyde 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

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 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.00032 mg/day. This exposure is 4375 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US 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, 2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde 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 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde 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. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde 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	3.93	3.93
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 0.004695 μg/L. The revised PEC/PNECs for EU and NA are not applicable; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 05/18/21.

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
- **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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	4.695			1000000	0.004695	

&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 12/10/21.

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.

Appendix F. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2022.113023.

Appendix

Read-across Justification

Methods

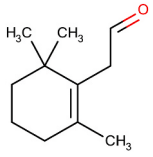
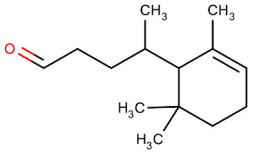
The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017a).

- 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde	4-(2,6,6-Trimethyl-2-cyclohexen)-2-methylbutanal
CAS No.	472-66-2	65405-84-7
Structure		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
		
Similarity (Tanimoto score)		0.64
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_{11}H_{18}O$	$C_{14}H_{24}O$
Molecular Weight	166.27	208.35
Melting Point (°C, EPI Suite)	30.89	43.04
Boiling Point (°C, EPI Suite)	232.55	270.68
Vapor Pressure (Pa @ 25 °C, EPI Suite)	7.65	0.834
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.93	5.20
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	28.31	1.442
J_{max} (mg/cm^2/h, SAM)	52.404	8.641
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.69E-004	9.31E-004
Skin Sensitization		
Protein binding by OASIS v1.4	• Schiff base formation	• Schiff base formation
Protein binding by OECD	• Schiff base formers	• Schiff base formers
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.4	• Schiff base formation	• Schiff base formation
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat liver S9 metabolism simulator and structural alerts for metabolites		

Summary

There are insufficient toxicity data on the target material 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde (CAS # 472-66-2). Hence *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7) was identified as a read-across material with data for the skin sensitization endpoint.

Conclusion

- The material, 4-(2,6,6-trimethyl-2-cyclohexen)-2-methylbutanal (CAS # 65405-84-7), was used as a read-across analog for the target material 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde (CAS # 472-66-2) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic aldehydes.
  - o The target material and the read-across analog share an aldehyde functional group and methyl-substituted cyclohexene ring.
  - o The key difference between the target material and the read-across analog is that the target has a shorter aliphatic chain between the aldehyde group and the cyclohexene ring compared to the read-across analog. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$ 80% skin absorption for the target material, $\leq$40% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target material and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The CAESAR model for skins sensitization predicts the target material and the read-across analog to be sensitizers with good reliability. Other skin sensitization endpoint alerts are consistent between the target material and the read-across analog. This shows that the 2 share comparable or similar reactivity. The data described in the skin sensitization section above shows that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alerts will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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