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RIFM fragrance ingredient safety assessment, 7-methoxy-3,7-dimethyloct-1-ene, CAS Registry Number 53767-86-5

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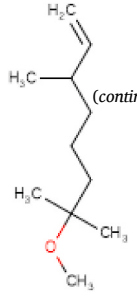

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CAS Registry Number: 53767-86-5

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., 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.

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

7-Methoxy-3,7-dimethyloct-1-ene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 7-methoxy-3,7-dimethyloct-1-ene is not genotoxic. The repeated dose and reproductive toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to 7-methoxy-3,7-dimethyloct-1-ene is above the TTC (0.0015 mg/kg/day); therefore, it is recommended that products containing 7-methoxy-3,7-dimethyloct-1-ene are limited to the maximum acceptable concentrations provided in Section X. Read-across to dihydromyrcenol (CAS # 18479-58-8) show that there are no safety concerns for 7-methoxy-3,7-dimethyloct-1-ene for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 7-methoxy-3,7-dimethyloct-1-ene is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material; exposure to 7-methoxy-3,7-dimethyloct-1-ene is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 7-methoxy-3,7-dimethyloct-1-ene was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2017a; RIFM, 2017b)
Repeated Dose Toxicity: No NOAEL available. Exposure is above the TTC; therefore, it is recommended that products containing 7-methoxy-3,7-dimethyloct-1-ene are limited to the maximum acceptable concentrations provided in Section X.
Reproductive Toxicity: No NOAEL available. Exposure is above the TTC; therefore, it is recommended that products containing 7-methoxy-3,7-dimethyloct-1-ene are limited to the maximum acceptable concentrations provided in Section X.
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. (RIFM, 2007; RIFM, 1996; RIFM, 1994a; RIFM, 1994b; RIFM, 2006)
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: 2.6 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 260.4 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2.974 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: 2.974 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.002974 μg/L
Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 7-Methoxy-3,7-dimethyloct-1-ene
2. **CAS Registry Number:** 53767-86-5
3. **Synonyms:** 1-Octene, 7-methoxy-3,7-dimethyl-; Dihydromyrcenyl methyl ether; 7-Methoxy-3,7-dimethyloct-1-ene
4. **Molecular Formula:** $C_{11}H_{22}O$
5. **Molecular Weight:** 170.29 g/mol
6. **RIFM Number:** 5732
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 172.31 °C (EPI Suite)
2. **Flash Point:** 63 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.17 (EPI Suite)
4. **Melting Point**: -32.29 °C (EPI Suite)

5. **Water Solubility:** 16.97 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.34 mm Hg at 20 °C (EPI Suite v4.0), 1.88 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 v3.1.4)

1. **95**th **Percentile Concentration in AirFresh Plugins*****:** 10% (RIFM, 2021b)
   (No reported use in Fine Fragrance)
2. **Inhalation Exposure*:** 0.0039 mg/kg/day or 0.22 mg/day (RIFM, 2021b)
3. **Total Systemic Exposure**:** 0.0039 mg/kg/day (RIFM, 2021b)

*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; 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; Comiskey et al., 2017).

***IFRA Category 4 in Section X for maximum acceptable concentrations in finished products.

5. Derivation of systemic absorption

1. **Dermal:** 2.9% SABS

SABS testing on 7-methoxy-3,7-dimethyloct-1-ene [RIFM, 2021a]: An *in vitro* human skin absorption study for 7-methoxy-3,7-dimethyloct-1-ene (CAS # 53767-86-5) was conducted following OECD TG 428 with application of 1% w/v (50 μg/cm^2 dose in 5 μL) in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions for 24 h. For both unoccluded and occluded conditions, 12 active-dosed diffusion cells were prepared in addition to 4 control cells (unoccluded conditions). At the end of 24 h, 2.19% ± 0.13% (= 1.09 ± 0.06 μg/cm^2) and 0.952% ± 0.203% (= 0.475 ± 0.102 μg/cm^2) of the applied dose permeated through the skin under unoccluded and occluded conditions, respectively. These values represent the worst-case scenario as the total 7-methoxy-3,7-dimethyloct-1-ene found in the epidermis, filter paper membrane support, receptor fluid, and SC tape strips 2–10. Overall recovery was 0.907% ± 0.214% and 32.4% ± 3.5% under unoccluded and occluded conditions, respectively.

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High* (Expert Judgment)

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

*See Appendix for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Dihydromyrcenol (CAS # 18479-58-8)
   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

7-Methoxy-3,7-dimethyloct-1-ene 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

HYPERLINK "https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/22301/1/2" \o "https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/22301/1/2" Available; accessed on 08/12/21 (ECHA, 2018).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 7-methoxy-3,7-dimethyloct-1-ene 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)	0.000010
2	Products applied to the axillae	0.000010
3	Products applied to the face/body using fingertips	0.000010
4	Products related to fine fragrances	0.000010
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.042
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.000010
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.000010
5D	Baby cream, oil, talc	0.0000033
6	Products with oral and lip exposure	0.000010
7	Products applied to the hair with some hand contact	0.000010
8	Products with significant ano-genital exposure (tampon)	0.0000033
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.0042
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.000010
10B	Aerosol air freshener	0.61
11	Products with intended skin contact but minimal transfer of fragrance to	0.0000033

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	skin from inert substrate (feminine hygiene pad)	
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.10

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 7-methoxy-3,7-dimethyloct-1-ene, the basis was the Cramer Class III threshold values for systemic toxicity.
[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 v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 7-methoxy-3,7-dimethyloct-1-ene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 7-Methoxy-3,7-dimethyloct-1-ene 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, 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 7-methoxy-3,7-dimethyloct-1-ene 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 7-methoxy-3,7-dimethyloct-1-ene in ethanol at concentrations up to 5000 μg/plate. An increase in the mean number of revertant colonies was observed in strain WP2uvrA in the absence of S9 in the first study (RIFM, 2017a). However, this 2.2-fold increase was not dose-responsive, was within the 95% historical control limit, and was not reproduced in the second study. Due to this, the increase was not considered biologically relevant. Under the conditions of the study, 7-methoxy-3,7-dimethyloct-1-ene was not mutagenic in the Ames test.

The clastogenic activity of 7-methoxy-3,7-dimethyloct-1-ene 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 7-methoxy-3,7-dimethyloct-1-ene in ethanol at concentrations up to 1700 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 170 μg/mL in the presence and absence of metabolic activation. 7-Methoxy-3,7-dimethyloct-1-ene did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, 7-methoxy-3,7-dimethyloct-1-ene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 7-methoxy-3,7-dimethyloct-1-ene does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 7-methoxy-3,7-dimethyloct-1-ene or any read-across materials. The total systemic exposure to 7-methoxy-3,7-dimethyloct-1-ene is above the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use. Therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X, which are based on the Cramer Class III threshold values.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 7-methoxy-3,7-dimethyloct-1-ene or on any read-across materials that can be used to support the repeated dose toxicity endpoint. After refinement based on 2.9% skin absorption rate determined by an *in vitro* study (see Section V), the total systemic exposure to 7-methoxy-3,7-dimethyloct-1-ene (3.9 μg/kg/day) is above the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use. As such, in the absence of data, it is recommended that products containing 7-methoxy-3,7-dimethyloct-1-ene are limited to the maximum acceptable concentrations provided in Section X. This will ensure that the total systemic exposure to this material falls below the TTC of 1.5 μg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/08/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 7-methoxy-3,7-dimethyloct-1-ene or any read-across materials. The total systemic exposure to 7-methoxy-3,7-dimethyloct-1-ene is above the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use. Therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X, which are based on the Cramer Class III threshold values.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 7-methoxy-3,7-dimethyloct-1-ene or on any read-across materials that can be used to support the reproductive toxicity endpoint. After refinement based on 2.9% skin absorption rate determined by an *in vitro* study (see Section V), the total systemic exposure to 7-methoxy-3,7-dimethyloct-1-ene (3.9 μg/kg/day) is above the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use. As such, in the absence of data, it is recommended that products containing 7-methoxy-3,7-dimethyloct-1-ene are limited to the maximum acceptable concentrations provided in Section X. This will ensure that the total systemic exposure to this material falls below the TTC of 1.5 μg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/08/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to dihydromyrcenol (CAS # 18479-58-8), 7-methoxy-3,7-dimethyloct-1-ene does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 7-methoxy-3,7-dimethyloct-1-ene. Based on the existing data and read-across material dihydromyrcenol (CAS # 18479-58-8; see Section VI), 7-methoxy-3,7-dimethyloct-1-ene is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material dihydromyrcenol was found to have low reactivity to skin proteins in the direct peptide reactivity assay (DPRA) (RIFM, 2016). In another DPRA, dihydromyrcenol showed minimal peptide depletion (RIFM, 2020c). Read-across material dihydromyrcenol was not predicted to be a sensitizer in KeratinoSens (RIFM, 2020b). In murine local lymph node assays

(LLNA), read-across material dihydromyrcenol was found to be non-sensitizing when tested up to 25% (6250 μg/cm^2) and 30% (7500 μg/cm^2), respectively (RIFM, 2007; RIFM, 1996). In guinea pig maximization tests and a Buehler test, an isomer of the read-across material, dihydromyrcenol (7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv.; CAS # 53219-21-9), did not present reactions indicative of sensitization (RIFM, 1994a; RIFM, 1994b). In a human maximization test, no skin sensitization reactions were observed with 4% (2760 μg/cm^2) read-across material dihydromyrcenol (RIFM, 1973). In a Confirmation of No Induction in Humans test (CNIH) with 2500 μg/cm^2 of 7-methoxy-3,7-dimethyloct-1-ene in alcohol SD 39C, no reactions indicative of sensitization were observed in any of the 51 volunteers (RIFM, 1990). In a CNIH with 20% (23,620 μg/cm^2) read-across material dihydromyrcenol in diethyl phthalate (DEP), no reactions indicative of sensitization were observed in any of the 109 volunteers (RIFM, 1995). Additionally, in a CNIH with 20% (23,620 μg/cm^2) 7-octen-2-ol, 2-methyl-6-methylene-, dihydro deriv. in 1:3 alcohol SD39C:DEP, no reactions indicative of sensitization were observed in 99 volunteers (RIFM, 2006).

Based on weight of evidence (WoE) from structural analysis, human studies, and read-across material dihydromyrcenol, 7-methoxy-3,7-dimethyloct-1-en does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1975; RIFM, 1972; RIFM, 1964; RIFM, 2001; RIFM, 2002.

Literature Search and Risk Assessment Completed On: 07/27/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 7-methoxy-3,7-dimethyloct-1-ene 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 7-methoxy-3,7-dimethyloct-1-ene 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, 7-methoxy-3,7-dimethyloct-1-ene 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: 07/26/21.

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 7-methoxy-3,7-dimethyloct-1-ene 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 7-methoxy-3,7-dimethyloct-1-ene. Based on the Creme RIFM Model, the inhalation exposure is 0.22 mg/day. This exposure is 2.1 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/20/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 7-methoxy-3,7-dimethyloct-1-ene was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional volume of use, log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ) expressed as the ratio: Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). In Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class-specific ecotoxicity estimates) is used allowing for a lower uncertainty factor to be applied to the PNEC. 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 of the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated based on the actual regional tonnage and not the extremes of the range. Following the RIFM Environmental Framework, 7-methoxy-3,7-dimethyloct-1-ene 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 7-methoxy-3,7-dimethyloct-1-ene 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 criteria used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite models BIOWIN 2 or BIOWIN 6 $<$ 0.5 and BIOWIN 3 $<$ 2.2, then the material is considered as potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. Should additional assessment be required, based on these model outputs (Step 1), a WoE-based review is 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 ver.4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 7-methoxy-3,7-dimethyloct-1-ene does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.3.3. Other available data. 7-Methoxy-3,7-dimethyloct-1-ene has been registered for REACH with no additional data at this time (ECHA, 2018).

11.2.4. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.974			1000000	0.002974	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.17	4.17
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 0.002974 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 volumes of use.

Literature Search and Risk Assessment Completed On: 07/26/21.

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&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 02/17/22.

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.2022.113097.

Appendix

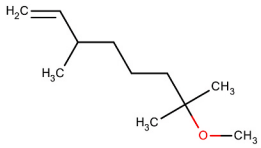
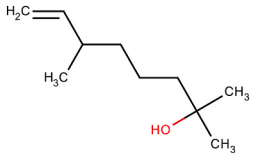
Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow 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, 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- 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	7-Methoxy-3,7-dimethyloct-1-ene	Dihydromyrcenol
CAS No.	53767-86-5	18479-58-8
Structure		
Similarity (Tanimoto Score)		0.62
Endpoint		Skin Sensitization
Molecular Formula	$C_{11}H_{22}O$	$C_{10}H_{20}O$
Molecular Weight (g/mol)	170.30	156.27
Melting Point (°C, EPI Suite)	−32.29	−13.10
Boiling Point (°C, EPI Suite)	172.31	191.28
Vapor Pressure (Pa @ 25 °C, EPI Suite)	250.65	16.53
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	16.97	252.20
Log K_{OW}	4.17	3.47
J_{max} (μg/cm^2/h, SAM)	2.57	29.70
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	833.90	4.12
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified.	No skin sensitization reactivity domain alerts were identified.
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 is insufficient toxicity data on 7-methoxy-3,7-dimethyloct-1-ene (CAS # 53767-86-5). Hence *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, dihydromyrcenol (CAS # 18479-58-8) was identified as a read-across material with data for the respective toxicity endpoint.

Conclusion

- Dihydromyrcenol (CAS # 18479-58-8) was used as a read-across analog for the target material, 7-methoxy-3,7-dimethyloct-1-ene (CAS # 53767-86-5), for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the generic class of unsaturated hydrocarbons.
  - o The key difference between the target material and the read-across analog is that the target material has a terminal methoxy group whereas the read-across analog has a terminal hydroxy group. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the benzene fragment. 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 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 read-across analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? Yes.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? Yes.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes.
Q22. A common component of food? No.
Q33. Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No.

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