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Short Review

RIFM fragrance ingredient safety assessment, sssmenthadiene-7-methyl formate, CAS registry number 68683-20-5

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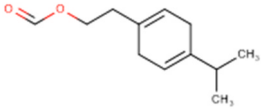
Name: Menthadiene-7-methyl formate
CAS Registry Number: 68,683-20-5



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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 Confirmation of No Induction in Humans 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)

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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.

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

Menthadiene-7-methyl formate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that menthadiene-7-methyl formate 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 menthadiene-7-methyl formate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data provided menthadiene-7-methyl formate a No Expected Sensitization Induction Level (NESIL) of 1000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; menthadiene-7-methyl formate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; menthadiene-7-methyl formate 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 VoU) 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, 2017b; RIFM, 2017a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 1000 μg/cm^2 (RIFM, 2007)
Photoirritation/Photoallergenicity: Not photoirritating/photoallergenic. (UV/Vis Spectra, RIFM Database; RIFM, 1979c; RIFM, 2018)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence:
Critical Measured Value: 80.2% (BODIS) (RIFM, 1996)
Bioaccumulation:
Screening-level: 288.5 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 3.01 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: 3.01 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00301 μg/L
•**Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Menthadiene-7-methyl formate
2. **CAS Registry Number:** 68,683-20-5
3. **Synonyms:** Cyclohexadiene-1-ethanol, 4-(1-methylethyl)-, formate; Isobergamate; 2-(4-Isopropylcyclohexadienyl)ethyl formate; 4-(Isopropyl)cyclohexadiene-1-ethyl formate; Menthadienyl formate; 4-(1-Methylethyl)cyclohexadiene-1-ethyl formate; Isobergamat; Menthadiene-7-methyl formate
4. **Molecular Formula:** $C_{12}H_{18}O_2$
5. **Molecular Weight:** 194.27 g/mol
6. **RIFM Number:** 1241
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 253.24 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.23 (EPI Suite)
4. **Melting Point**: 33.96 °C (EPI Suite)
5. **Water Solubility:** 11.35 mg/L (EPI Suite)
6. **Specific Gravity:** 0.9910 (RIFM)
7. **Vapor Pressure:** 0.0187 mm Hg at 25 °C (EPI Suite), 0.0107 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Absorbance between 290 and 700 nm, with a peak at 260 nm and returning to baseline by 340 nm. Molar absorption coefficients under the biologically relevant neutral condition and the acidic condition (572 and 582 L mol^{-1} • cm^{-1} respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}); the molar absorption coefficient for the acidic condition (2931 L mol^{-1} • cm^{-1}) is above the benchmark
9. **Appearance/Organoleptic:** A colorless to slightly yellow liquid

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.025% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000069 mg/kg/day or 0.0046 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0035 mg/kg/day (RIFM, 2021)

*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).

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 v4.5
I	I	I

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

7. Metabolism

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

8. Natural occurrence

Menthadiene-7-methyl formate 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 01/12/22

10. Conclusion

The maximum acceptable concentrations[a] in finished products for menthadiene-7-methyl formate are detailed below

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.077
2	Products applied to the axillae	0.023
3	Products applied to the face/body using fingertips	0.46
4	Products related to fine fragrances	0.43
5 A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.11
5 B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.11
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.11
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.25
7	Products applied to the hair with some hand contact	0.88
8	Products with significant ano-genital exposure (tampon)	0.045
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.84
10 A	Household care products with mostly hand contact (hand dishwashing detergent)	3.0
10 B	Aerosol air freshener	3.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.7
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 menthadiene-7-methyl formate, the basis was a skin sensitization NESIL of 1000 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, menthadiene-7-methyl formate does not present a concern for genotoxicity.

11.1.2. Risk assessment

Menthadiene-7-methyl formate was assessed in the Bluescreen assay and found positive for cytotoxicity (positive: <80% relative cell density; at the highest concentration tested of 625 μM) without metabolic activation, negative for cytotoxicity (negative: >80% relative cell density) with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2014). BlueScreen is a human

cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of menthadiene-7-methyl formate 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 menthadiene-7-methyl formate 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 concentration in the presence or absence of S9 (RIFM, 2017b). Under the conditions of the study, menthadiene-7-methyl formate was not mutagenic in the Ames test.

The clastogenic activity of menthadiene-7-methyl formate 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 menthadiene-7-methyl formate in DMSO at concentrations up to 1940 μg/mL in the dose range finding (DRF) study, and micronuclei analysis was conducted at concentrations up to 290 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. Menthadiene-7-methyl formate 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, 2017a). Under the conditions of the study, menthadiene-7-methyl formate was non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, menthadiene-7-methyl formate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.3. Repeated dose toxicity

There are no repeated dose toxicity data on menthadiene-7-methyl formate or any read-across materials. The total systemic exposure to menthadiene-7-methyl formate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no repeated dose toxicity data on menthadiene-7-methyl formate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to menthadiene-7-methyl formate (3.5 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: 01/12/22.

11.1.4. Reproductive toxicity

There are insufficient reproductive toxicity data on menthadiene-7-methyl formate or any read-across materials. The total systemic exposure to menthadiene-7-methyl formate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.4.1. Risk assessment. There are no reproductive toxicity data on menthadiene-7-methyl formate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to menthadiene-7-methyl formate (3.5 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: 01/12/22.

11.1.5. Skin sensitization

Based on the available data, menthadiene-7-methyl formate is a skin sensitizer with a defined NESIL of 1000 μg/cm^2 and the maximum acceptable concentrations are provided in Section X.

11.1.5.1. Risk assessment. Based on the existing data, menthadiene-7-methyl formate is considered a sensitizer with a defined NESIL of 1000 μg/cm^2 (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.5; Toxtree v3.1.0). Menthadiene-7-methyl formate was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA) and KeratinoSens (RIFM, 2015b; RIFM, 2015a). Further, in a murine local lymph node assay (LLNA), menthadiene-7-methyl formate was not found to be sensitizing up to a concentration of 10% (2500 μg/cm^2) (RIFM, 2008). In 3 human maximization tests, skin sensitization reactions were observed at 10% (6900 μg/cm^2) of menthadiene-7-methyl formate in 1/25, 4/29, and 3/25 subjects, respectively (RIFM, 1977; RIFM, 1978a; RIFM, 1978b). However, in the follow-up human maximization tests conducted at 1.5% (unknown patch size) and 1% (690 μg/cm^2), no reactions indicative of sensitization were observed (RIFM, 1979b; RIFM, 1979a). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 0.9% (1063 μg/cm^2) of menthadiene-7-methyl formate in 3:1 diethyl phthalate:ethanol, no reactions indicative of sensitization were observed in any of the 101 volunteers tested (RIFM, 2007).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, animal studies, and human studies, menthadiene-7-methyl formate is a sensitizer with a WoE NESIL of 1000 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/20/22.

11.1.6. Photoirritation/photoallergenicity

Based on UV/Vis absorption spectra and available *in vitro* and *in vivo* study data, menthadiene-7-methyl formate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.6.1. Risk assessment. UV spectra indicate absorbance in the critical range of 290–700 nm, with a peak at 260 nm and returning to baseline by 340 nm. The molar absorption coefficients are below the benchmark of concern for photoirritation/photoallergenicity under the biologically relevant neutral condition, as well as the acidic condition. Under the basic condition, the molar absorbance was above the benchmark (Henry et al., 2009). A 3T3-Neutral Red Uptake photoirritation assay (OECD TG 432) was performed with menthadiene-7-methyl formate, and according to the prediction model presented in the OECD test guidelines, it was not predicted to have photoirritating potential (RIFM, 2018). In a guinea pig photoallergy study, the application of 1.5% menthadiene-7-methyl formate in white petrolatum did not result in any skin reactions. Based on UV/Vis absorbance under the biologically relevant neutral condition and available study data, menthadiene-7-methyl formate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.6.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were generated for menthadiene-7-methyl formate. The spectra demonstrate that the material absorbs in the range of 290–700 nm, with a peak at 260 nm and returning to baseline by 340 nm. The molar absorption coefficients within this range (572 and 582 L mol^{-1} • cm^{-1} under the biologically relevant neutral condition and the acidic

Table 1
Summary of existing data on menthadiene-7-methyl formate.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal 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	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
Moderate	1063	690	6900	1000	>2500	NA	NA
	In vitro Data[e]				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Positive	Positive	NA		No alert found	Radical reactions	No alert found

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

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Studies conducted according to the OECD TG 406 are included in the table.

[e] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

condition, respectively) are below 1000 L mol^{-1} • cm^{-1}, the benchmark of concern for photoirritating effects (Henry et al., 2009). The molar absorption coefficient for the acidic condition (2931 L mol^{-1} • cm^{-1}) was above the benchmark of concern for photoirritating effects.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/18/22.

11.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for menthadiene-7-methyl formate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are no inhalation data available on menthadiene-7-methyl formate. Based on the Creme RIFM Model, the inhalation exposure is 0.0046 mg/day. This exposure is 304.3 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: 01/19/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of menthadiene-7-methyl formate 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, menthadiene-7-methyl formate 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) did not identify menthadiene-7-methyl formate as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api 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, 2017). 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 VoU (2019), menthadiene-7-methyl formate presents a 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 using the BODIS test method. Biodegradation of 80.2% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Menthadiene-7-methyl formate has been pre-registered for REACH, with no additional data available 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.01			1000000	0.00301	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.23	4.23
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 0.00301 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: 05/22/22.

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
  - **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
  - **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 ChemView:** https://chemview.epa.gov/chemview/
  - **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 12/05/22.

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.

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