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Short Review

RIFM fragrance ingredient safety assessment, 4,8-dimethyl-7-nonen-2-ol, CAS registry number 40596-76-7

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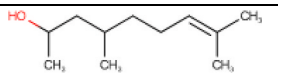

Name: 4,8-Dimethyl-7-nonen-2-ol
CAS Registry Number: 40596-76-7
Additional CAS Number*:
379693-55-7
7-Nonen-2-ol, 4,8-dimethyl-, (4S)- (No Reported Use)
*Included because the materials are isomers

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
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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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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

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OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

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

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

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

4,8-Dimethyl-7-nonen-2-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4,8-dimethyl-7-nonen-2-ol is not genotoxic. Data on read-across material 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The 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 4,8-dimethyl-7-nonen-2-ol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3) show that there are no safety concerns for 4,8-dimethyl-7-nonen-2-ol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 4,8-dimethyl-7-nonen-2-ol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4,8-dimethyl-7-nonen-2-ol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2004a; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 167 mg/kg/day.	RIFM (2004c)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.	
Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.	RIFM (2003)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEL available. Exposure is below TTC.	

Environmental Safety Assessment

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Hazard Assessment:	
Persistence:	
Screening-level: 2.98 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 194.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 4.44 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 4.44 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.00444 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

Chemical Name: 4,8-Dimethyl-7-nonen-2-ol	Chemical Name: 7-Nonen-2-ol, 4,8-dimethyl-, (4S)-
CAS Registry Number: 40596-76-7	**CAS Registry Number:** 379693-55-7
Synonyms: 4,8-Dimethylnon-7-en-2-ol; Homocitronellol; 脂肪族不飽和アルコール (C = 9 ~ 24); 7-Nonen-2-ol, 4,8-dimethyl-; Hedirosa; 4,8-Dimethyl-7-nonen-2-ol	**Synonyms:** (4S)-4,8-Dimethyl-7-nonen-2-ol; 7-Nonen-2-ol, 4,8-dimethyl-, (4S)-
Molecular Formula: $C_{11}H_{22}O$	**Molecular Formula:** $C_{11}H_{22}O$
Molecular Weight: 170.29 g/mol	**Molecular Weight:** 170.29 g/mol
RIFM Number: 6369	**RIFM Number:** 6369
Stereochemistry: Isomer not specified. Two chiral centers present and 4 total enantiomers possible.	**Stereochemistry:** 4S isomer specified. Two chiral centers present and 4 total enantiomers possible.

2. Physical data

See

CAS # 40596-76-7	CAS # 379693-55-7
Boiling Point: 229.58 °C (EPI Suite)	**Boiling Point:** 241.55 °C (EPI Suite)
Flash Point: 103 °C (Globally Harmonized System)	**Flash Point:** Not Available
Log K_{OW}: 3.97 (EPI Suite)	**Log K_{OW}:** 3.17 (EPI Suite)
Melting Point: −13.63 °C (EPI Suite)	**Melting Point**: 9.49 °C (EPI Suite)
Water Solubility: 80.28 mg/L (EPI Suite)	**Water Solubility:** 274 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.0071 mm Hg at 20 °C (EPI Suite v4.0), 0.0119 mm Hg at 25 °C (EPI Suite), 1.59 Pa at 25 °C (WSKOW v1.42 in EPI Suite)	**Vapor Pressure:** 0.745 Pa at 25 °C (WSKOW v1.42 in EPI Suite)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)	**UV Spectra:** Not Available
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

See

1.0.1–1 metric ton per year	IFRA (2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)***

1.95th Percentile Concentration in Fine Fragrance: 0.22%	RIFM (2016b)
2. Inhalation Exposure*: 0.00018 mg/kg/day or 0.012 mg/day	RIFM (2016b)
3. Total Systemic Exposure**: 0.0027 mg/kg/day	RIFM (2016b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics or 95th percentile, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

Cramer Classification: Class I, Low.

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

1. Analogs Selected:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity**: 1-(2-Methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3)
   c. **Reproductive Toxicity**: None
   d. **Skin Sensitization**: 1-(2-Methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
2. **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 (discrete chemical) or composition (NCS)

4,8-Dimethyl-7-nonen-2-ol and 7-nonen-2-ol, 4,8-dimethyl-, (4S)- are 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

4,8-Dimethyl-7-nonen-2-ol has been pre-registered for 2010.7-Nonen-2-ol, 4,8-dimethyl-, (4S)-, 379693-55-7 has not been pre-registered. No dossier available for either material as of 06/10/20.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 4,8-dimethyl-7-nonen-2-ol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 4,8-dimethyl-7-nonen-2-ol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 4,8-dimethyl-7-nonen-2-ol 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, 2004a). Under the conditions of the study, 4,8-dimethyl-7-nonen-2-ol was not mutagenic in the Ames test.

The clastogenic activity of 4,8-dimethyl-7-nonen-2-ol 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 4,8-dimethyl-7-nonen-2-ol in DMSO at concentrations up to 1703 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 256 μg/mL in the presence and absence of metabolic activation. 4,8-Dimethyl-7-nonen-2-ol did not induce binucleated cells with micronuclei when tested up to cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, 4,8-dimethyl-7-nonen-2-ol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 4,8-dimethyl-7-nonen-2-ol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/02/20.

11.1.2. Repeated dose toxicity

The MOE for 4,8-dimethyl-7-nonen-2-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4,8-dimethyl-7-nonen-2-ol. Read-across material 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 407 and GLP-compliant study, 5 Sprague Dawley CrI:CD (SD) IGS BR rats/sex/dose were orally administered the test material through gavage at doses of 0 (Arachis oil), 15, 150, and 500 mg/kg/day for 28 days. Recovery groups of 5 animals/sex/dose were maintained for an additional 14 days for the 0 and 500 mg/kg/day groups. No treatment-related adverse effects were reported for any of the tested parameters in any treatment group. Thus, the NOAEL for repeated dose toxicity was

considered to be 500 mg/kg/day (RIFM, 2004c).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 500/3, or 167 mg/kg/day.

Therefore, the 4,8-dimethyl-7-nonen-2-ol MOE can be calculated by dividing the NOAEL for 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol by the total systemic exposure to 4,8-dimethyl-7-nonen-2-ol, 167/0.0027, or 61852.

In addition, the total systemic exposure to 4,8-dimethyl-7-nonen-2-ol (2.7 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/15/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4,8-dimethyl-7-nonen-2-ol or any read-across materials. The total systemic exposure to 4,8-dimethyl-7-nonen-2-ol 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 4,8-dimethyl-7-nonen-2-ol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (2.7 μg/kg/day) is below the TTC for 4,8-dimethyl-7-nonen-2-ol (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/26/20.

11.1.4. Skin sensitization

Based on the existing data and read-across material 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3), 4,8-dimethyl-7-nonen-2-ol presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 4,8-dimethyl-7-nonen-2-ol. Based on the existing data and read-across material 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3; see Section VI), 4,8-dimethyl-7-nonen-2-ol is not considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol was not found to be sensitizing when tested up to 100% (RIFM, 2003). In guinea pig maximization tests, 4,8-dimethyl-7-nonen-2-ol did not present reactions indicative of sensitization (RIFM, 2004b; RIFM, 1976). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 20% 4,8-dimethyl-7-nonen-2-ol in white petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1979).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol, 4,8-dimethyl-7-nonen-2-ol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/26/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4,8-dimethyl-7-nonen-2-ol 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 4,8-dimethyl-7-nonen-2-ol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 4,8-dimethyl-7-nonen-2-ol 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 significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/29/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4,8-dimethyl-7-nonen-2-ol 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 4,8-dimethyl-7-nonen-2-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 117 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/15/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4,8-dimethyl-7-nonen-2-ol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4,8-dimethyl-7-nonen-2-ol 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 4,8-dimethyl-7-nonen-2-ol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for

a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 4,8-dimethyl-7-nonen-2-ol presents no 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.

11.2.3. Other available data

4,8-Dimethyl-7-nonen-2-ol has been pre-registered for REACH with no additional data available at this time.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.97	3.97
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.

*Combined regional Volumes of Use for both CAS #s.

The RIFM PNEC is 0.00444 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: 06/24/20.

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 09/30/20.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	4.44			1000000	0.00444	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111995.

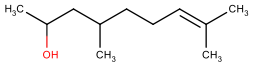
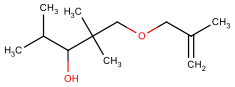
Appendix

Read-across Justification

Methods

The read-across analogs were identified using the RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). 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, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), 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, 2020).
- 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	4,8-Dimethyl-7-nonen-2-ol	1-(2-Methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol
CAS No.	40596-76-7	526218-21-3
Structure		
Similarity (Tanimoto Score)		0.05
Endpoint		• Repeated dose toxicity • Skin sensitization
Molecular Formula	$C_{11}H_{22}O$	$C_{12}H_{24}O_2$
Molecular Weight (g/mol)	170.296	200.322
Melting Point (°C, EPI Suite)	−13.63	9.49
Boiling Point (°C, EPI Suite)	229.58	241.55
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.59E+00	7.45E-01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	8.03E+01	2.74E+02
Log KOW	3.97	3.17
J_{max} (μg/cm^2/h, SAM)	11.04	10.53
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.63E+00	4.77E-02
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
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 domains alerts identified	No skin sensitization reactivity domains alerts 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 are insufficient toxicity data on 4,8-dimethyl-7-nonen-2-ol (CAS # 40596-76-7). 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, 1-(2-methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3) was identified as a read-across analog with sufficient data for

toxicological evaluation.

Conclusions

- 1-(2-Methylprop-2-enoloxy)-2,2,4-trimethylpentan-3-ol (CAS # 526218-21-3) was used as a read-across analog for the target material 4,8-dimethyl-7-nonen-2-ol (CAS # 40596-76-7) for the skin sensitization and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class branched aliphatic secondary alcohols.
  - o The target material and the read-across analog share a secondary hydroxy group.
  - o The key differences between the target material and the read-across analog are in their branched and alkyl chain structure. In addition, the read-across analog has a vinyl group compared to the vinylene in the target material. This group is less hindered compared to the vinylene and so will undergo an oxidation reaction yielding epoxide faster and with more probability compared to the vinylene in the target material. Therefore, the read-across analog is predicted to have more reactivity compared to the target material. The read-across analog also has an ether linkage in the aliphatic chain. The target material does not have an ether linkage. This ether link is predicted to be inert for reactivity related to skin sensitization and repeated dose toxicity. Therefore, these structural differences are toxicologically insignificant for the skin sensitization and repeated dose toxicity endpoints.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a 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 There are no alerts for the skin sensitization or the repeated dose toxicity endpoints. Therefore, the *in silico* alerts are consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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