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Short review

RIFM fragrance ingredient safety assessment, 3,7-dimethyl-1,6-nonadien-3-ol, CAS Registry Number 10339-55-6

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ABSTRACT

The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog linalool (CAS # 78-70-6) show that this material is not genotoxic nor does it have skin sensitization potential and also provided a MOE > 100 for the local respiratory endpoint. The repeated dose, developmental and reproductive toxicity endpoints were completed using nerolidol (isomer unspecified, CAS # 7212-44-4) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

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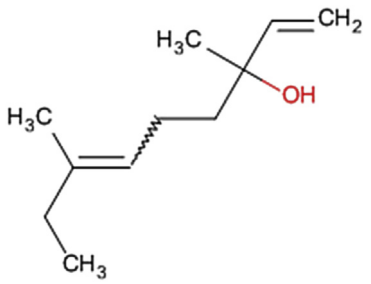

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable 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
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
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence
RIFM's Expert Panel* concludes that this material is safe under the limits 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog linalool (CAS # 78-70-6) show that this material is not genotoxic nor does it have skin sensitization potential and also provided a MOE > 100 for the local respiratory endpoint. The repeated dose, developmental and reproductive toxicity endpoints were completed using nerolidol (isomer unspecified, CAS # 7212-44-4) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not Genotoxic (RIFM, 2002; RIFM, 2001a)
Repeated Dose Toxicity: NOAEL = 35 mg/kg/day (RIFM, 2010b)
Developmental and Reproductive Toxicity: NOAEL = 266 and 705 mg/kg/day respectively (RIFM, 2010b)
Skin Sensitization: Not sensitizing (RIFM, 1975; Greif, 1967; RIFM, 1970)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 63 mg/m^3 (RIFM, 2012a)
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 91% (RIFM, 2006b)

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(*continued*)

Bioaccumulation: Screening Level: 166.7 L/kg (EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 72 h Algae EC50: 6.4 mg/L (RIFM, 2013)
Conclusion: Not PBT or vPvB as per Environmental Standards
Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 72 h Algae EC50: 6.4 mg/L (RIFM, 2013)
RIFM PNEC is: 6.4 μg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** 3,7-Dimethyl-1,6-nonadien-3-ol
2. **CAS Registry Number:** 10339-55-6
3. **Synonyms:** 3,7-Dimethyl-1,6-nonadien-3-ol; Ethyl linalool (so called); 1,6-Nonadien-3-ol, 3,7-dimethyl-; 脂肪族不飽和アルコール (C = 9~24); 3,7-Dimethylnona-1,6-dien-3-ol
4. **Molecular Formula:** $C_{11}H_{20}O$
5. **Molecular Weight:** 168.28
6. **RIFM Number:** 668

2. Physical data

1. **Boiling Point:** 223.32 °C [EPI Suite]
2. **Flash Point:** 177 °F; CC [FMA database]
3. **Log K_{OW}:** 3.2 at 35 °C [RIFM, 1997b], 3.3 at 35 °C [RIFM, 1997b], 3.87 [EPI Suite]
4. **Melting Point**: −0.13 °C [EPI Suite]
5. **Water Solubility:** 99.98 mg/L [EPI Suite]
6. **Specific Gravity:** 0.866 [FMA database]
7. **Vapor Pressure:** 0.0106 mm Hg @ 20 °C [EPI Suite 4.0], 0.02 mm Hg 20 °C [FMA database], 0.0177 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless slightly oily liquid which has a floral, only slightly woody-green, soft odor of moderate tenacity.

3. Exposure

1. **Volume of Use (worldwide band):** 10−100 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.90% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0023 mg/kg/day or 0.17 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.026 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2015).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

Expert judgment	Toxtree v.2.6	OECD QSAR toolbox v.3.1
I*	III	II

*See Appendix below for explanation.

2. **Analogs Selected:**
   a. **Genotoxicity:** Linalool (CAS # 78-70-6)
   b. **Repeated Dose Toxicity:** Nerolidol (isomer unspecified, CAS # 7212-44-4)
   c. **Developmental and Reproductive Toxicity:** Nerolidol (isomer unspecified, CAS # 7212-44-4)
   d. **Skin Sensitization:** Linalool (CAS # 78-70-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Linalool (CAS # 78-70-6)
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurrence (discrete chemical) or composition (NCS)

3,7-Dimethyl-1,6-nonadien-3-ol is not reported to occur in food 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, contains information on published volatile

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compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed on 08/27/13

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3,7-dimethyl-1,6-nonadien-3-ol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The genotoxic potential of 3,7-dimethyl-1,6-nonadien-3-ol has been evaluated for mutagenicity in bacteria. Five *S. typhimurium* tester strains used showed 3,7-dimethyl-1,6-nonadien-3-ol to be not mutagenic in any tester strain either with or without metabolic activation in an Ames assay, conducted according to OECD TG 471 (RIFM, 2002).

There are no other available data for 3,7-dimethyl-1,6-nonadien-3-ol; however, read-across to linalool (CAS # 78-70-6; see Section 5), another member of the RIFM category: Alcohol/Branched chain/Unsaturated/Tertiary α,β- provides sufficient support for the clastogenicity endpoint. The Fragrance Material Review on linalool, summarizes the data available at the time, including negative Ames studies in *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537, TA1538, and *E. coil* strain WP2uvrA, a negative sister chromatid exchange assay in CHO cells, a negative test for induction of unscheduled DNA synthesis in rat primary hepatocytes, and a negative *in vivo* mouse micronucleus assay (Letizia et al., 2003). While one mouse lymphoma assay demonstrated a weak positive result for linalool, the authors emphasized that positive results in this assay are commonly observed for polar substances in the presence of S9 and may be associated with changes in physiologic culture conditions such as pH and osmolality (Heck et al., 1989). When a second mouse lymphoma study was conducted which took into account cytotoxicity, osmolality and pH, the results were negative (RIFM, 1994a). Linalool has previously been reviewed by RIFM's Expert Panel and it was concluded that there is sufficient mutagenicity and clastogenicity data indicating the material is not genotoxic (Belsito et al., 2010). Since this evaluation by the Panel, an *in vitro* micronucleus test demonstrated negative effects for linalool (DiSotto et al., 2011) further supporting a lack of genotoxic concern for linalool, which can be extended to 3,7-dimethyl-1,6-nonadien-3-ol.

Based on the data available, 3,7-dimethyl-1,6-nonadien-3-ol does not present a concern for genotoxic potential.

10.1.1.2. Additional References. None.

10.1.1.3. Literature Search and Risk Assessment Completed on:
05/17/13.

10.1.2. Repeated dose toxicity

The margin of exposure for 3,7-dimethyl-1,6-nonadien-3-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3,7-dimethyl-1,6-nonadien-3-ol. Read across material nerolidol (isomer unspecified, CAS # 7212-44-4; see Section 5) has an OECD 422 dietary combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats (RIFM, 2010b). The NOAEL for females was determined to be 1500 ppm (105, 120 or 193 mg/kg bw/day in non-pregnant, pregnant or lactating females, respectively), based on reductions in food consumption and body weights, clinical pathological changes, increased liver weights, central hepatocellular hypertrophy, and central fatty change. The NOAEL for males was determined to be 4000 ppm (266 mg/kg bw/day), based on reductions in food consumption and body weights, clinical pathological changes, and increased liver weights.

A default safety factor of 3 was used when deriving a NOAEL from the 28 day or OECD 422/421/407 studies. The safety factor has been approved by RIFM's Independent Expert Panel*.

Thus the derived NOAEL for the repeated dose toxicity data is 105/3 or 35 mg/kg/day.

Therefore, the MOE is equal to the nerolidol (isomer unspecified) NOAEL for non-pregnant females in mg/kg/day divided by the total systemic exposure, 35/0.026 or 1346.

In addition, the total systemic exposure for 3,7-dimethyl-1,6-nonadien-3-ol (26 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

10.1.2.2. Additional References. McGinty et al., 2010a; Belsito et al., 2010; OECD SIDS, 1995a,b: 3-Buten-2-ol, 2-methyl-; McGinty et al., 2010c; RIFM, 1994b; RIFM, 1980; Politano et al., 2008; RIFM, 2006a; Letizia et al., 2007; RIFM, 2007a, 2007b, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003; Lapczynski et al., 2008a, 2008b, 2008c; Bickers et al., 2003; Belsito et al., 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012a; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982, 1984; RIFM, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959, 1965; Lapczynski et al., 2008d; Hanley et al., 1997; Blair et al., 2000; OECD SIDS, 1995a,b: Isophytol; McGinty et al., 2010b; Cal and Sznitowska, 2003; Cal, 2006; Cal and Kryzaniak, 2006b.

10.1.2.3. Literature Search and Risk Assessment Completed on:
05/17/13.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3,7-dimethyl-1,6-nonadien-3-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 3,7-dimethyl-1,6-nonadien-3-ol. Read across material nerolidol (isomer unspecified, CAS # 7212-44-4; see Section 5) has an OECD 422 dietary combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats (RIFM, 2010b). The NOAEL for developmental toxicity was

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determined to be 4000 ppm (266 mg/kg bw/day in males and 279, 340 or 468 mg/kg bw/day in non-pregnant, pregnant or lactating females, respectively), based on reduced growth and development of offspring. These effects occurred at maternally toxic dosages. **Therefore, the MOE for developmental toxicity is equal to the nerolidol (isomer unspecified) NOAEL for males in mg/kg/day divided by the total systemic exposure, 266/0.026 or 10231.**

There are no reproductive toxicity data on 3,7-dimethyl-1,6-nonadien-3-ol. Read across material nerolidol (isomer unspecified, CAS # 7212-44-4) has an OECD 422 dietary combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats (RIFM, 2010b). The NOAEL for fertility and reproductive performance in males and females was determined to be $\geq$ 12000 ppm (758 mg/kg bw/day in males and 705, 824 or 1194 mg/kg bw/day in non-pregnant, pregnant or lactating females, respectively), the highest dosage tested. **Therefore, the MOE for reproductive toxicity is equal to the nerolidol (isomer unspecified) NOAEL for non-pregnant females in mg/kg/day divided by the total systemic exposure, 705/0.026 or 27115.**

In addition, the total systemic exposure to 3,7-dimethyl-1,6-nonadien-3-ol (26 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoint.

10.1.3.2. Additional References. McGinty et al., 2010a; Belsito et al., 2010; OECD SIDS, 1995a,b: 3-Buten-2-ol, 2-methyl-; McGinty et al., 2010c; RIFM, 1994b; RIFM, 1980; Politano et al., 2008; RIFM, 2006a; Letizia et al., 2007; RIFM, 2007a; RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003; Lapczynski et al., 2008a, 2008b, 2008c; Bickers et al., 2003; Belsito et al., 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012a; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madyastha, 1982, 1984; RIFM, 1998; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959, 1965; Lapczynski et al., 2008d; Hanley et al., 1997; Blair et al., 2000; OECD SIDS, 1995a,b: Isophytol; McGinty et al., 2010b.

10.1.3.3. Literature Search and Risk Assessment Completed on: 05/17/13.

10.1.4. Skin sensitization

Based on existing data for 3,7-dimethyl-1,6-nonadien-3-ol and the read across material linalool (CAS # 78-70-6), 3,7-dimethyl-1,6-nonadien-3-ol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the weight of evidence when taking into account the limited data specific to 3,7-dimethyl-1,6-nonadien-3-ol and read across material (linalool, CAS # 78-70-6; see Section 5), 3,7-dimethyl-1,6-nonadien-3-ol does not present a concern for skin sensitization. The chemical structure of each material indicates that they would not have the potential to act as skin sensitizers (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.0)*. While positive responses to linalool have been reported in Guinea pig test methods (Ishihara et al., 1986; Klecak, 1979, 1985; Sharp, 1978) and the LLNA (i.e., Basketter et al., 2002a; and Basketter et al., 2002b); these results have been attributed to autoxidation products and the irritant potential of linalool (RIFM, 2010a; Skold et al., 2004, Skold et al., 2002). An analogous autoxidation would be expected to take place for 3,7-dimethyl-1,6-nonadien-3-ol (OECD toolbox v3.0, Natsch et al., 2013). Human confirmatory studies have resulted in no sensitization reactions with 3,7-dimethyl-1,6-nonadien-3-ol and linalool (RIFM, 1975; Greif, 1967; RIFM, 2005; RIFM, 1970).

*Note: Whereas linalool is considered to be a non-sensitizer, autoxidation products of this material are known to be contact allergens. Linalool, and natural products rich in linalool, are subject to an IFRA standard that defines a good manufacturing practice (GMP) specification limiting peroxide levels to 20 mmol/l with a recommendation to add an antioxidant at the time of production (IFRA, 2009). Similarly, as predicted by OECD toolbox (v3.0), an analogous autoxidation would be expected to take place for 3,7-dimethyl-1,6-nonadien-3-ol and could result in autoxidation products with a sensitization potential.

10.1.4.2. Additional References. None.

10.1.4.3. Literature Search and Risk Assessment Completed on: 05/17/13.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 3,7-dimethyl-1,6-nonadien-3-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3,7-dimethyl-1,6-nonadien-3-ol in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of significant absorbance in the critical range, 3,7-dimethyl-1,6-nonadien-3-ol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. Additional References. None.

10.1.5.3. Literature Search and Risk Assessment Completed on: 07/19/16.

10.1.6. Local respiratory toxicity

The margin of exposure for 3,7-dimethyl-1,6-nonadien-3-ol is adequate for the respiratory endpoint at the current level of use.

10.1.6.1. Risk assessment. There are no inhalation data available on 3,7-dimethyl-1,6-nonadien-3-ol; however, in an acute, two week inhalation study for the analog linalool (CAS # 78-70-6; see Section 5), a NOAEC of 63 mg/m^3 was reported by RIFM, 2012a. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a two week, acute inhalation study conducted in rats, a NOAEC of 63 mg/m^3 was reported for linalool (RIFM, 2012a). Test substance-related effects were limited to non-adverse microscopic findings in the nasal cavity. This NOAEC expressed in mg/kg lung weight/day is:

- (63 mg/m^3) (1m^3/1000 L) = 0.063 mg/L

- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.063 mg/L) (61.2 L/day) = 3.86 mg/day
- (3.86 mg/d)/(0.0016 kg lung weight of rat*) = 2412.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.17 mg/day - this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.26 mg/kg lung weight/day resulting in a MOE of 9279 (i.e., [2412.5 mg/kg lung weight/day]/[0.26 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.17 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed. 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: “Comparative Physiology and Anatomy”, subsection, “Comparative Airway Anatomy.”

10.1.6.2. Additional References. RIFM, 1977; Jirovetz et al., 1991; Buchbauer et al., 1991; RIFM, 1997a; Buchbauer et al., 1993; Perrucci et al., 1996; Perrucci, 1995; Rice and Coats, 1994b; Silver, 1992; Karr and Coats, 1992; Regnault-Roger and Hamraoui, 1995; Rice and Coats, 1994a; Perrucci et al., 1995b; Sugawara et al., 1998; Coats et al., 1991; Cometto-Muniz et al., 1998; Isola et al., 2003a; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003b; Isola et al., 2003b; Isola et al., 2004a; Larsen et al., 1997; Smith et al., 2004; RIFM, 2004; Isola et al., 2004b; Barocelli et al., 2004; Rogers et al., 2005; Kuroda et al., 2005; Tanida et al., 2006; Yang et al., 2005; Corsi et al., 2007; Sato et al., 2007; Nakamura et al., 2010; Nakamura et al., 2009; de Moura Linck et al., 2009

10.1.6.3. Literature Search and Risk Assessment Completed on: 07/20/16.

11. Environmental endpoint summary

11.1. Screening-level assessment

A screening level risk assessment of 3,7-dimethyl-1,6-nonadien-3-ol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or 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. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 3,7-dimethyl-1,6-nonadien-3-ol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did identify 3,7-dimethyl-1,6-nonadien-3-ol as being possibly persistent but not bio-accumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2. Risk assessment

Based on current Volume of Use (2011), 3,7-dimethyl-1,6-nonadien-3-ol presents a risk to the aquatic compartment.

11.3. Key studies

11.3.1. Biodegradation

RIFM, 2006b: A study was conducted following OECD Test Guideline 301F. 100 mg/l of the test substance was incubated for a period of 28 days. The test material underwent 91% biodegradation after 28 days.

11.3.2. Ecotoxicity

RIFM, 2013: A static algae growth inhibition study was conducted following OECD Test Guideline 201 using *Pseudokirchneriella subcapitata*. Based on the reported test concentrations the 72 h EC50 values were EbC50of 16 mg/l and EC50 (cell density) and EyC50: 6.4 mg/l. The NOEC was 0.29 mg/l.

RIFM, 2012c: A flow-through *Daphnia magna* immobilization study following OECD Test Guideline 202 was reported. The reported 48 h EC50 (mean measured) was 32 mg/l.

RIFM, 2012b: A flow-through acute fish toxicity study was performed using *Pimephales promelas* following OECD Test Guideline 203. The reported 96 h LC50 (mean measured) was 18 mg/l.

11.4. Other available data

This material has been pre-registered under REACH. No additional data are available at this time.

11.5. 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.

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	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	16.2 mg/l			1,000,000	0.0162 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.710 mg/l	0.278 mg/l	2.030 mg/l	10,000	0.0278 μg/l	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.878 mg/l	1.942 mg/l	2.957 mg/l			Neutral Organic

Tier 3: Measured Data

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	18 mg/l					
Daphnia		32 mg/l				
Algae		6.4 mg/l	0.29 mg/l	1,000	6.4 μg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.3	3.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	<1	<1

Based on available data, the RQ for this class of material is <1. No further assessment is necessary.

The RIFM PNEC is 6.4 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 05/17/13.

12. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

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*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

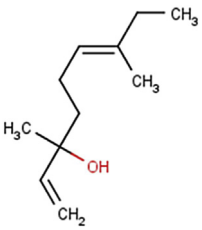
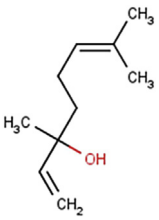
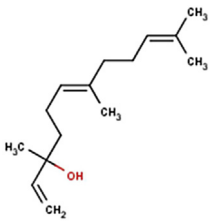
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.09.024.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.09.024.

Appendix

	Target material	Read across material	
Principal Name	3,7-Dimethyl-1,6-nonadien-3-ol	Linalool	Nerolidol (isomer unspecified)
CAS No.	10339-55-6	78-70-6	7212-44-4
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/10339-55-6.html	http://www.thegoodscentscompany.com/opl/78-70-6.html	http://www.thegoodscentscompany.com/opl/7212-44-4.html
Read-across endpoint		• Genotoxicity • Skin sensitization • Respiratory	• Repeated Dose • Devel/Repro
Molecular Formula	C11H20O	C10H18O	C15H26O
Molecular Weight	168.28	154.25	222.37
Melting Point (°C, EPISUITE)	−0.13	−11.39	20.98
Boiling Point (°C, EPISUITE)	223.32	204.05	291.92
Vapor Pressure (Pa @ 25°C, EPISUITE)	2.36	11.09	0.07893
Log Kow (KOWWIN v1.68 in EPISUITE)	3.87	3.38	5.68
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	99.98	683.7	1.532
J_{max} (mg/cm^2/h, SAM)	18.82631309	90.06108298	1.58778939
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	5.688385	4.285034	18.339825
Similarity (Tanimoto score)[1]		82%	83%
In silico Results for Target and Analog			
Genotoxicity			
DNA binding (OASIS v1.1)	• No alert found	• No alert found	
DNA binding (OECD)	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found	
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts (ISS)	• No alert found	• No alert found	
Oncologic classification (OECD)	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized		Not categorized
Developmental and Reproductive Toxicity			
ER binding (OECD)	Non binder, non cyclic structure		Non binder, non cyclic structure
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (low reliability)		NON-Toxicant (low reliability)
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 (OECD)	• 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 model (CAESAR v2.1.5)	NON-Sensitizer (low reliability)	Sensitizer (experimental activity)	
Metabolism			
Rat liver S9 metabolism simulator (OECD)	10339-55-6 pdf	78-70-6 pdf	7212-44-4 pdf

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint. J. Chem. Inf. Model. Rogers and Hahn, 2010.

Summary

There are insufficient toxicity data on 3,7-dimethyl-1,6-nonadien-3-ol (RIFM # 668, CAS # 10339-55-6). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Linalool (analog) was used as a read-across analog for 3,7-dimethyl-1,6-nonadien-3-ol (target) based on:
- The target and analog belong to the generic class of alcohols, specifically, alcohol/branched chain/unsaturated/tertiary α,β.
- The target and analog are terpene alcohol. They have the same number isoprene units and hydroxyl group.
- The only difference is that the target has an additional methyl group at the terminal. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
- The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
- The target and analog show similar alerts for protein binding.
- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- Nerolidol (isomer unspecified) (analog) was used as a read-across for 3,7-dimethyl-1,6-nonadien-3-ol (target) based on:
- The target and analog belong to the generic class of alcohols, specifically, alcohol/branched chain/unsaturated/tertiary α,β.
- The target and analog are terpene alcohol. They have the isoprene units and hydroxyl group.
- The key difference is that the analog have an additional isoprene unit than the target. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
- The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.

Explanation of Cramer class

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., 1976).

Q1. Normal constituent of the body? **No**.

Q2. Contains functional groups associated with enhanced toxicity? **No**.

Q3. Contains elements other than C,H,O,N,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? **No**.

Q17. Readily hydrolysed to a common terpene? **No**.

Q19. Open chain? **Yes**.

Q20. Aliphatic with some functional groups? **Yes**.

Q21. Does the structure contain three or more different types of functional groups (exclude methoxy and consider acids and esters as one functional type)? **No**.

Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **No**: Class Low (Class I).

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