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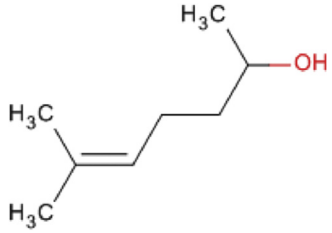
Short Review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 2-Methyl-2-hepten-6-ol, CAS Registry Number 1569-60-4

A.M. Api[a], D. Belsito[b], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St, Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil*
[g] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239, USA*
[i] *Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr, Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 051618. This version replaces any previous versions.



Name: 2-Methyl-2-hepten-6-ol
CAS Registry Number: 1569-60-4

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
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

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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
QRA - Quantitative Risk Assessment
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 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 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 use of this material under current conditions is supported by existing information.

2-Methyl-2-hepten-6-ol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, and environmental safety. Data show that 2-methyl-2-hepten-6-ol is not genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The repeated dose toxicity, developmental and reproductive toxicity, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to 2-methyl-2-hepten-6-ol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 2-methyl-2-hepten-6-ol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-methyl-2-hepten-6-ol was not found to be PBT as per IFRA environmental standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2004; RIFM, 2015)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.1 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)

Bioaccumulation: Screening-level: 23.16 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: Fish LC50: 55.18 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: 55.18 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.0552 μg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe NA; Cleared at the screening-level

1. Identification

1. **Chemical Name:** 2-Methyl-2-hepten-6-ol
2. **CAS Registry Number:** 1569-60-4
3. **Synonyms:** 5-Hepten-2-ol, 6-methyl-; 6-Hydroxy-2-methyl-2-heptene; 6-Methylhept-5-en-2-ol; Methyl heptenol; 2-Methyl-2-hepten-6-ol
4. **Molecular Formula:** $C_8H_{16}O$
5. **Molecular Weight:** 128.15
6. **RIFM Number:** 5251

2. Physical data

1. **Boiling Point:** 182.59 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.57 (EPI Suite)
4. **Melting Point:** −36.75 °C (EPI Suite)
5. **Water Solubility:** 1919 mg/L (EPI Suite)
6. **Specific Gravity:** 0.84800 to 0.85400 @ 25.00 °C*
7. **Vapor Pressure:** 0.211 mm Hg @ 20 °C (EPI Suite v4.0), 0.324 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless clear liquid with a medium, sweet, oily, green, coriander odor at 1.00% solution or less*

*http://www.thegoodscentscompany.com/data/rw1008971.html, retrieved 9/14/13.

3. Exposure

1. **Volume of Use (worldwide band):** < 1 metric tons per year (IFRA, 2011)

2. **95th Percentile Concentration in Hydroalcoholics:** 0.0040% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000018 mg/kg/day or 0.0014 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.000033 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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, 2017; Safford et al., 2015, 2017).

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 II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	I	II

2. *Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.
3. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: None
   d. Skin Sensitization: 4,8-Dimethyl-7-nonen-2-ol (CAS # 40596-76-7)
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
4. Read-across Justification: See Appendix below

6. Metabolism

Not relevant for this risk assessment.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

2-Methyl-2-hepten-6-ol is reported to occur in the following foods by the VCF*:

Annatto (Bixa orellana L.)
Apple brandy (calvados)
Apple fresh (Malus species)
Buckwheat
Cider (apple wine)
Citrus fruits
Dalieb, palmyra palm fruit (Borassus aethiopum L.)
Ginger (Zingiber species)
Grape brandy
Guava wine
Honey
Lemon balm (Melissa officinalis L.)
Litchi (Litchi chinensis Sonn.)
Loganberry juice (Rubus ursinus var. Loganobaccus)
Macadamia nut (Macadamia integrifolia)
Passion fruit (Passiflora species)
Pulasan (Nephelium ramboutan-ake (Labill.) Leenh.)
Raspberry, blackberry, and boysenberry
Starfruit (Averrhoa carambola L.)
Strawberry (Fragaria species)
Syzygium species
Tomato (Lycopersicon esculentum Mill.)
Wine

*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 that contains information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 05/16/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the available data, 2-methyl-2-hepten-6-ol does not present a concern for genotoxic potential.

10.1.1.1. Risk assessment. 2-Methyl-2-hepten-6-ol was tested using the BlueScreen assay and found negative for both cytotoxicity and genotoxicity indicating a lack for genotoxic concern (RIFM, 2014). The mutagenic activity of 2-methyl-2-hepten-6-ol was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with 2-methyl-2-hepten-6-ol in dimethyl sulfoxide (DMSO) at the concentrations of at 33, 100, 333, 1000, 2500, and 5000 μg/plate in the presence and absence of metabolic activation. 2-Methyl-2-hepten-6-ol did not produce statistically significant increases in revertant colony numbers in the tester strains at the concentrations tested (RIFM, 2004). Under the conditions of the study, 2-methyl-2-hepten-6-ol was considered not mutagenic in the Ames test.

The clastogenic activity of 2-methyl-2-hepten-6-ol was assessed in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-methyl-2-hepten-6-ol at concentrations up to 1280 μg/mL in the presence and absence of metabolic activation. The percentage of cells with micronucleated binucleated cells in the test substance-treated groups was not statistically significantly increased relative to vehicle control at any dose level (RIFM, 2015). Under the conditions of the study, 2-methyl-2-hepten-6-ol was considered non-clastogenic in human peripheral lymphocytes.

Based on the available data, 2-methyl-2-hepten-6-ol does not present a concern for genotoxic potential.

Additional References: None

Literature Search and Risk Assessment Completed On: 5/5/2017

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-methyl-2-hepten-6-ol or any read-across materials. The total systemic exposure to 2-methyl-2-hepten-6-ol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-methyl-2-hepten-6-ol or any read-across material that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-methyl-2-hepten-6-ol (0.033 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 04/28/2017

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 2-methyl-2-hepten-6-ol or any read-across materials. The total systemic exposure to 2-methyl-2-hepten-6-ol is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 2-methyl-2-hepten-6-ol or any read-across material that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to 2-methyl-2-hepten-6-ol (0.033 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 04/28/2017

10.1.4. Skin sensitization

Based on the available data for the read-across material 4,8-dimethyl-7-nonen-2-ol (CAS # 40596-76-7) and application of DST, 2-methyl-2-hepten-6-ol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data for the read-across analog 4,8-dimethyl-7-nonen-2-ol (CAS # 40596-76-7; see Section V), 2-methyl-2-hepten-6-ol does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13; OECD Toolbox v3.4). While there are no experimental studies available for 2-methyl-2-hepten-6-ol, in guinea pig test methods and a confirmatory human study, no reactions indicative of sensitization were observed with the read-across material 4,8-dimethyl-7-nonen-2-ol (RIFM, 1976; RIFM, 2004). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford et al., 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentrations for 2-methyl-2-hepten-6-ol which present no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None

Literature Search and Risk Assessment Completed On: 09/06/13

10.1.5. Phototoxicity/photoallergenicity

Based on UV absorption spectra, 2-methyl-2-hepten-6-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 2-methyl-2-hepten-6-ol in experimental models. UV absorption spectra indicate no significant absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 2-methyl-2-hepten-6-ol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no significant absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None

Literature Search and Risk Assessment Completed On: 05/01/17

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-methyl-2-hepten-6-ol is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-methyl-2-hepten-6-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.0014 mg/day. This exposure is 336 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Additional References: None

Literature Search and Risk Assessment Completed On: 5/8/2017

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-2-hepten-6-ol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-methyl-2-hepten-6-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 v4.1 did not identify 2-methyl-2-hepten-6-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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then

Table 1
Acceptable concentration limits for 2-methyl-2-hepten-6-ol based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.07%	0%
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.00%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.03%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), 2-methyl-2-hepten-6-ol does not present a risk to the aquatic compartment.

10.2.3. Key studies

None

10.2.3.1. Biodegradation. None

10.2.3.2. Ecotoxicity. None

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

10.2.4. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L)

Endpoints used to calculate PNEC are highlighted.

Exposure	Europe (EU)	North America (NA)
Log Kow Used	2.57	2.57
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 the available data, the RQ for this class of material is < 1. No further assessment is necessary

The RIFM PNEC is 0.0552 µg/L. The PEC/PNECs for EU and NA: not applicable; cleared at screening-level, and therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 5/2/17

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	55.18			1,000,000	0.0552	

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

- **NTP:** https://ntp.niehs.nih.gov/
- 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://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.07.040.

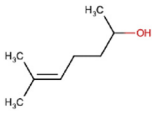
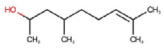
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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 substance and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read-across material
Principal Name	2-Methyl-2-hepten-6-ol	4,8-Dimethyl-7-nonen-2-ol
CAS No.	1569-60-4	40596-76-7
Structure		
Similarity (Tanimoto score)		0.84
Read-across endpoint		• Skin sensitization
Molecular Formula	$C_8H_{16}O$	$C_{11}H_{22}O$
Molecular Weight	128.22	170.3
Melting Point (°C, EPI Suite)	−36.75	−13.63
Boiling Point (°C, EPI Suite)	182.59	229.58
Vapor Pressure (Pa @ 25°C, EPI Suite)	43.2	1.59
Log Kow (KOWWIN v1.68 in EPI Suite)	2.57	3.97
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1919	80.28
J_{max} (mg/cm^2/h, SAM)	151.922	24.515
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.22E-005	7.53E-005
Skin Sensitization		
Protein Binding by OASIS v1.1	• No alert found	• No alert found
Protein Binding by OECD	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify	• Not possible to classify

Protein Binding Alerts for Skin Sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization Model (CAESAR) (v2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (v3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites		

Summary

There are insufficient toxicity data on the 2-methyl-2-hepten-6-ol (CAS # 1569-60-4). Therefore, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 4,8-dimethyl-7-nonen-2-ol (CAS # 40596-76-7) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusion

- 4,8-Dimethyl-7-nonen-2-ol (CAS # 40596-76-7) was used as a read-across analog for the target material 2-methyl-2-hepten-6-ol (CAS # 1569-60-4) for the skin senzitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the structural class of alcohols.
  - The target substance and the read-across analog share a heptene fragment.
  - The key difference between the target substance and the read-across analog is that the target substance is a 7-membered unsaturated branched alcohol while the read-across analog is a 9-membered unsaturated branched alcohol. This structural difference between the target substance and the read-across analog is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the unsaturated, branched alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the skin sensitization endpoint are consistent between the target substance and the read-across analog.
  - According to the CAESAR model for skin sensitization, the read-across analog and the target substance are predicted to be sensitizers. The data described in the skin sensitization section above show that the read-across analog does not pose a concern for skin sensitization. Therefore, the alert will be superseded by the availability of the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are toxicologically insignificant.

Explanation of Cramer Classification

Due to potential discrepancies between 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.

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 (see explanation in Cramer et al., 1978)? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open-chain? **Yes**
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? **Yes**
Q21. 3 or more different functional groups? **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) **Yes,** Intermediate (Class II)

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M.,, Benfenati, E., 2010, July. CAESAR models for developmental toxicity. Chemistry Central Journal 4 (S1), S4 Springer International Publishing.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2011. Volume of Use Survey, 2011.
OECD, 2012. The OECD QSAR Toolbox, v 3.4. Retrieved from. http://www.qsartoolbox.org/.
OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
RIFM (Research Institute for Fragrance Materials, Inc), 1976. Screening Test for Delayed Contact Hypersensitivity with 7-nonen-2-ol, 4,8-dimethyl- in the Albino guinea Pig. Unpublished Report from Firmenich Incorporated. RIFM report number 38741. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004a. Salmonella typhimurium reverse Mutation Assay with 1,2,3,4,4a,7,8,8a-octahydro-2,4a,5,8a-tetramethyl-1-naphthyl Formate (Oxyoctaline Formate). Unpublished Report from Givaudan. RIFM report number 44311. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004b. Toxicity Studies with 7-nonen-2-ol, 4,8-dimethyl- in guinea Pigs and Rats. Unpublished Report from Takasago International Corporation. RIFM report number 46339. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2014. Report on the Testing of 2-methyl-2-hepten-6-ol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 67046. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015. 2-Methyl-2-hepten-6-ol: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 69544. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 13. November 2016.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015b. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J.,., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.