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Short Review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 4,8-Dimethyl-3-7-nonadien-2-ol, CAS Registry Number 67845-50-5

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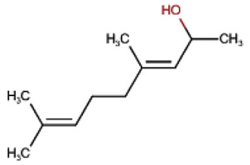

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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
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

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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.

4,8-Dimethyl-3-7-nonadien-2-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, and environmental safety. Data from read-across analog 4-methyl-3-decen-5-ol (CAS# 81782-77-6) show that 4,8-dimethyl-3-7-nonadien-2-ol is not expected to be genotoxic. Data show that 4,8-dimethyl-3-7-nonadien-2-ol is not a safety concern at the current, declared levels of use for the skin sensitization endpoint. The repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to 4,8-dimethyl-3-7-nonadien-2-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; 4,8-dimethyl-3-7-nonadien-2-ol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4,8-dimethyl-3-7-nonadien-2-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, 2002; RIFM, 2015a)

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

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

Skin Sensitization: Not a sensitization concern (RIFM, 2004a,c)

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: 2.9 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)

Bioaccumulation: Screening-level: 170 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 5.149 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: 5.149 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.005149 µg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe: not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name**: 4,8-Dimethyl-3-7-nonadien-2-ol
2. **CAS Registry Number**: 67845-50-5
3. **Synonyms**: (+/−)E− and Z-4,8-Dimethyl-3,7-nonadien-2-ol; 3,7-Nonadien-2-ol, 4,8-dimethyl- (E,Z)-; 4,8-Dimethylnona-3,7-dien-2-ol; 4,8-Dimethyl-3-7-nonadien-2-ol
4. **Molecular Formula**: Not Available
5. **Molecular Weight**: 168.28
6. **RIFM Number**: 6497

2. Physical data

1. **Boiling Point**: 70–72 °C at 2 mm Hg (Private communication to FEMA)
2. **Flash Point**: 208 °F (Private communication to FEMA)
3. **Log Kow**: 3.627*
4. **Melting Point**: Not Available
5. **Water Solubility**: Water, 97.04 mg/L @ 25 °C*
6. **Specific Gravity**: 0.860–0.870 (Private communication to FEMA)
7. **Vapor Pressure**: 0.00334 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium woody, pine, lemon, lime, rose, citronellol odor*

*http://www.thegoodscentscompany.com/data/rw1383291.html, retrieved 5/18/2017.

3. Exposure

1. **Volume of Use (worldwide band)**: 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.0030% (RIFM, 2014)
3. **Inhalation Exposure***: < 0.0001 mg/kg/day or < 0.0001 mg/day (RIFM, 2014)
4. **Total Systemic Exposure****: 0.00024 mg/kg/day (RIFM, 2014)

*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; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 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 I, Low

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

2. **Analogs Selected**:
   a. **Genotoxicity:** 4-methyl-3-decen-5-ol (CAS # 81782-77-6)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

4,8-Dimethyl-3-7-nonadien-2-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 containing 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 05/10/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the existing data, 4,8-dimethyl-3-7-nonadien-2-ol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 4,8-Dimethyl-3-7-nonadien-2-ol was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 4,8-dimethyl-3-7-nonadien-2-ol; however, read-across can be made to 4-methyl-3-decen-5-ol (CAS # 81782-77-6; see Section V). The mutagenic activity of 4-methyl-3-decen-5-ol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with 4-methyl-3-decen-5-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 dose in the presence or absence of S9 (RIFM, 2002). Under the conditions of the study, 4-methyl-3-decen-5-ol was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of 4,8-dimethyl-3-7-nonadien-2-ol; however, read-across can be made to 4-methyl-3-decen-5-ol (CAS # 81782-77-6). The clastogenic activity of 4-methyl-3-decen-5-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 4-methyl-3-decen-5-ol in DMSO at concentrations up to 1710 μg/mL in the presence and absence of metabolic activation. The percentage of micronucleated binucleated cells in the test substance-treated groups was not increased relative to vehicle control at any concentration level (RIFM, 2015a). Under the conditions of the study, 4-methyl-3-decen-5-ol was considered not clastogenic in human peripheral lymphocytes.

Based on the available data, 4-methyl-3-decen-5-ol does not present a concern for genotoxicity, and this can be extended to 4,8-dimethyl-3-7-nonadien-2-ol.

Additional References: RIFM, 2015b.

Literature Search and Risk Assessment Completed On: 5/6/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4,8-dimethyl-3-7-nonadien-2-ol or any read-across materials. The total systemic exposure to 4,8-dimethyl-3-7-nonadien-2-ol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4,8-dimethyl-3-7-nonadien-2-ol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 4,8-dimethyl-3-7-nonadien-2-ol (0.24 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

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

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4,8-dimethyl-3-7-nonadien-2-ol or any read-across materials. The total systemic exposure to 4,8-dimethyl-3-7-nonadien-2-ol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 4,8-dimethyl-3-7-nonadien-2-ol or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 4,8-dimethyl-3-7-nonadien-2-ol (0.24 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on 4,8-dimethyl-3-7-nonadien-2-ol or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to 4,8-dimethyl-3-7-nonadien-2-ol (0.24 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I 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 existing data, 4,8-dimethyl-3-7-nonadien-2-ol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, 4,8-dimethyl-3-7-nonadien-2-ol does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD Toolbox v3.4). In a murine local lymph node assay, 4,8-dimethyl-3-7-nonadien-2-ol was not found to be sensitizing up to the maximum tested level of 30% (7500 μg/cm^2) (RIFM, 2004a). Additionally, in confirmatory human repeat insult patch tests (HRIPT), no reactions were observed up to 12.5% (6887 μg/cm^2) 4,8-dimethyl-3-7-nonadien-2-ol in 3:1 ethanol:DEP (RIFM, 2004b,c). Based on the weight of evidence from structural analysis as well as animal and human data, 4,8-dimethyl-3-7-nonadien-2-ol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4,8-dimethyl-3-7-nonadien-2-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 4,8-dimethyl-3-7-nonadien-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 et al., 2009). Based on lack of absorbance, 4,8-Dimethyl-3-7-nonadien-2-ol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/25/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 4,8-dimethyl-3-7-nonadien-2-ol is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 4,8-dimethyl-3-7-nonadien-2-ol. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4,8-dimethyl-3-7-nonadien-2-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, 4,8-dimethyl-3-7-nonadien-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 v4.1 (US EPA, 2012a) did not identify 4,8-dimethyl-3-7-nonadien-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 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 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), 4,8-dimethyl-3-7-nonadien-2-ol does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 4,8-Dimethyl-3-7-nonadien-2-ol has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.149			1,000,000	0.005149	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.89	3.89
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 0.005149 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at the 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/
- **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.2018.07.008.

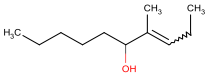
Appendix

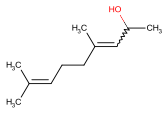
Read-across justification

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).
- Jmax 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.	67845-50-5	81782-77-6
Structure		

		
Similarity (Tanimoto Score)		0.798
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{11}H_{20}O$	$C_{11}H_{22}O$
Molecular Weight	168.28	170.30
Melting Point (°C, EPI Suite)	−12.25	−2.92
Boiling Point (°C, EPI Suite)	241.21	240.58
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.762	0.793
Log Kow (KOWWIN v1.68 in EPI Suite)	3.89	3.9[1]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	97.04	63[2]
J_{max} (mg/cm^2/h, SAM)	54.689	8.330
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.82E-005	7.53E-005
Genotoxicity		
DNA Binding (OASIS v1.4 QSAR Toolbox v3.4)	• No alert found	• No alert found
DNA Binding by OECD QSAR Toolbox (v3.4)	• No alert found	• No alert found
Carcinogenicity (Genotox and Non-Genotox Alerts by ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)
DNA Alerts for Ames, MN, CA by OASIS v1.1	• No alert found	• No alert found
In Vitro Mutagenicity (Ames test alerts by ISS)	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus Alerts by ISS)	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Metabolism		
OECD QSAR Toolbox (v3.4) Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites	See Supplemental Data 1	See Supplemental Data 2

[1] RIFM, 1996.
[2] RIFM, 2012.

Summary

There are insufficient toxicity data on the 2-methyl-2-hepten-6-ol (CAS # 67845-50-5). Hence, *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, analog 4-methyl-3-decen-5-ol (CAS # 81782-77-6) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusion

- 4-Methyl-3-decen-5-ol (CAS # 81782-77-6) was used as a read-across analog for target material 2-methyl-2-hepten-6-ol (CAS # 67845-50-5) for the genotoxicity 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 an alpha,beta-unsaturated aliphatic alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target is a 9-membered unsaturated aliphatic alcohol while the read-across analog is a 7-membered unsaturated aliphatic alcohol. This structural difference between the target substance and the read-across analog does not affect consideration of genotoxicity.
  - 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 aliphatic 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. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$80% skin absorption for the target substance and $\leq$40% absorption for the read-across analog. While percentage of skin absorption estimated from J_{max} values indicates exposure of the substance, it may or may not be toxicologically relevant. Therefore, the J_{max} of the target substance and the read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for genotoxicity are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for genotoxicity 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.

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