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Short Review

RIFM fragrance ingredient safety assessment, *trans*-2-Hexenol, CAS Registry Number 928-95-0

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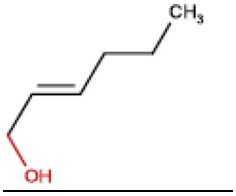
Version: 050118. This version replaces any previous versions.

Name: *trans*-2-Hexenol

CAS Registry Number: 928-95-0

Additional CAS Numbers:
2305-21-7 2-Hexen-1-ol



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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 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

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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
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.

trans-2-Hexenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic. The skin sensitization endpoint was completed by utilizing the DST for non-reactive materials. The local reproductive and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The repeated dose and developmental toxicity endpoints were completed by using 3-methyl-2-buten-1-ol (CAS # 556-82-1) as a read-across analog, which provided an MOE >100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2013b; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 65.4 mg/kg/day.	(RIFM, 2002b)
Developmental and Reproductive Toxicity: NOAEL = 600 mg/kg/day. Reproductive: No NOAEL available. Exposure is below the TTC.	(RIFM, 2002a)
Skin Sensitization: Not a sensitization concern. 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: 3.43 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 5.347 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 301.1 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: 301.1 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.3011 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level	

1. Identification

Chemical Name: *trans*-2-Hexenol	**Chemical Name**: 2-Hexen-1-ol
CAS Registry Number: 928-95-0	**CAS Registry Number:** 2305-21-7
Synonyms: 2-Hexenol, (E); アルケニルアルコール(C = 5–8); Hex-2-en-1-ol; *trans*-2-Hexenol	**Synonyms:** Hex-2-en-1-ol; 3-Propylallyl alcohol
Molecular Formula: $C_6H_{12}O$	**Molecular Formula:** $C_6H_{12}O$
Molecular Weight: 100.16	**Molecular Weight:** 100.16
RIFM Number: 298	**RIFM Number:** 5018

2. Physical data*

1. **Boiling Point:** 155 °C (FMA), 165.73 °C (EPI Suite)
2. **Flash Point:** 133°F; CC (FMA)
3. **Log K_{OW}:** log Pow = 1.6 (RIFM, 2013c), 1.61 (EPI Suite)
4. **Melting Point**: −38.47 °C (EPI Suite)
5. **Water Solubility:** 16000 mg/L (EPI Suite)
6. **Specific Gravity:** 0.839 (FMA)
7. **Vapor Pressure:** 0.608 mm Hg @ 20 °C (EPI Suite v4.0), 3.0 mm Hg

20C (FMA), 0.911 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Arctander Volume I 1969: A colorless liquid with a powerful, fruity-green-like odor

*Physical data is identical for both materials included in this assessment.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.026% (RIFM, 2014a)
3. **Inhalation Exposure*:** 0.000085 mg/kg/day or 0.0062 mg/day (RIFM, 2014a)
4. **Total Systemic Exposure**:** 0.00071 mg/kg/day (RIFM, 2014a)

*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).

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

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**: None
   b. **Repeated Dose Toxicity:** 3-Methyl-2-buten-1-ol (CAS # 556-82-1)
   c. **Developmental and Reproductive Toxicity**: 3-Methyl-2-buten-1-ol (CAS # 556-82-1)
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: none
3. **Read-across Justification**: None

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)

trans-2-Hexenol is reported to occur in the following foods by the VCF*:

Allium species.
Apple brandy (*Calvados*).
Apple fresh (*Malus* species).
Apple processed (*Malus* species).
Apricot (*Prunus armeniaca* L.).
Artichoke.
Avocado (*Persea americana* Mill.).
Babaco fruit (*Carica pentagona* Heilborn).
Banana (*Musa sapientum* L.).
Bilberry wine.
Black choke berry (*Aronia melanocarpa* Ell.).
Black currants (*Ribes nigrum* L.).
Brassica campestris.
Cabbage (*Brassica oleracea*).
Camomile.
Capsicum species.
Celery (*Apium graveolens* L.).
Cheese, various types.
Cherimoya (*Annona cherimolia* Mill.).
Cherry.
Chinese quince (*Pseudocydonia sinensis* Schneid).
Cider (apple wine).
Citrus fruits.
Cloudberry (*Rubus chamaemorus* L.).
Dill (*Anethum* species).
Elderberry (*Sambucus nigra* L.).
Endive (*Cichorium endivia* L.).
Ginger (*Zingiber* species).
Grape (*Vitis* species).
Grape brandy.
Guava and feyoa.
Katsuobushi (dried bonito).
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*).
Lamb's lettuce (*Valerianella locusta*).
Lettuce (*Lactuca sativa* L.).
Litchi (*Litchi chinensis* Sonn.).
Loquat (*Eriobotrya japonica* Lindl.).
Lovage (*Levisticum officinale* Koch).
Maize (*Zea mays* L.).
Malt.
Mangifera species.
Mastic (*Pistacia lentiscus*).
Mentha oils.
Milk and milk products.
Mulberry spirit (*Mouro*).
Nectarine.
Ocimum species.
Olive (*Olea europaea*).
Papaya (*Carica papaya* L.).
Peach (*Prunus persica* L.).
Pear brandy.
Peas (*Pisum sativum* L.).

Pistachio oil (*Pistacia vera*).
Plum (*Prunus*species).
Plum brandy.
Prickly pear (*Opuntia ficus indica*).
Quince, marmelo (*Cydonia oblonga*Mill.).
Radish (*Raphanus sativus* L.).
Rambutan (*Nephelium lappaceum*L.).
Raspberry, blackberry and boysenberry.
Red currants (*Ribes rubrum*L.).
Rice (*Oryza sativa*L.).
Rooibos tea (*Aspalathus linearis*).
Salvia species.
Sea buckthorn (*Hippophaërhamnoides* L.).
Soursop (*Annona muricata* L.).
Soybean (*Glycine max.* L. merr.).
Starfruit (*Averrhoa carambola* L.).
Strawberry (*Fragaria* species).
Strawberry wine.
Swiss cheese.
Syzygium species.
Tamarind (*Tamarindus indica* L.).
Tea.
Thyme (*Thymus* species).
Tomato (Lycopersicon esculentum Mill.).
Vaccinium species.
Wax gourd, winter melon (*Benincasa hispada* Cogn).
Whisky.
Wine.

2-Hexen-1-ol is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*).
Apple brandy (*Calvados*).
Apple processed (*Malus* species).
Asparagus (*Asparagus officinalis* L.).
Beef.
Beer.
Citrus fruits.
Dwarf Quince (*Chaenomeles japonica*).
Grape (*Vitis* species).
Grape brandy.
Honey.
Hop (*Humulus lupulus*).
Kiwifruit (*Actinidia chinensis,* syn. *A. deliciosa*).
Litchi (*Litchi chinensis* Sonn.).
Loquat (*Eriobotrya japonica* Lindl.).
Malt.
Olive (*Olea europaea*).
Peanut (*Arachis hypogaea* L.).
Plum (*Prunus* species).
Potato (*Solanum tuberosum* L.).
Prickly pear (*Opuntia ficus indica*).
Soybean (*Glycine max.* L. merr.).
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 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

trans-2-Hexenol and 2-hexen-1-ol are pre-registered for 2010; no dossiers available as of 05/01/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, *trans*-2-hexenol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. *trans*-2-Hexenol was assessed in the BlueScreen assay and was found negative for genotoxicity in the presence of S9 metabolic activation and positive for genotoxicity without S9 metabolic activation, indicating a concern for genotoxic potential (RIFM, 2013a). The mutagenic activity of *trans*-2-hexenol was assessed using the Ames mutagenicity assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. Coli* WP2uvrA were treated with *trans*-2-hexenol in dimethyl sulfoxide (DMSO) at concentrations of 1.5–5000 μg/plate in the presence and absence of S9 metabolic activation using the plate incorporation method. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2013b). Under the conditions of this study, *trans*-2-hexenol was considered not mutagenic.

The clastogenic potential of *trans*-2-hexenol was evaluated in an *in vitro* micronucleus test in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with *trans*-2-hexenol in DMSO at concentrations of 0.1–1000 μg/mL in the presence and absence of metabolic activation (S9) at the 4-h and 24-h time points. *trans*-2-Hexenol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014b). Under the conditions of the study, *trans*-2-hexenol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, *trans*-2-hexenol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/18/15.

10.1.2. Repeated dose toxicity

The margin of exposure for *trans*-2-hexenol 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 *trans*-2-hexenol. Read-across material, 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section V) has an enhanced OECD 408 oral (drinking water) 90-day subchronic toxicity study conducted in rats. Groups of 10 rats/sex/dose were administered 3-methyl-2-buten-1-ol in drinking water at concentrations of 0, 200, 1000, or 5000 ppm for 3 months (equivalent to 0, 14.4, 65.4 or 243.8 mg/kg/day for males and 0, 21.0,

82.1, or 307.2 mg/kg/day for females, respectively). The NOAEL was determined to be 1000 ppm, or 65.4 and 82.1 mg/kg/day for males and females, respectively, based on decreased body weight, food and water consumption, and urine volume among animals of the higher dose groups (RIFM, 2002b). Therefore, the *trans*-2-hexenol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-methyl-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to *trans*-2-hexenol, 65.4/0.00071 or 92113.

In addition, the total systemic exposure to *trans*-2-hexenol (0.71 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2010a,d; Hagan et al., 1967; Bar and Griepentrog, 1967; RIFM, 2010e,f; Gilpin et al., 2010; RIFM, 2008a,c; RIFM, 2001; RIFM, 1954; Vieira et al., 2011; Fielden et al., 2007; Hood et al., 1978; Abramovici and Feder, 1980; Abramovici, 1972; Forschmidt et al., 1979; Abramovici and Rachmuth-Roizman, 1983; Howes et al., 2002; Buchbauer et al., 1993; Chadha and Madyastha, 1984; King and Dickinson, 2000; King and Dickenson, 2003; Westfall et al., 1997; Piccinini, 1962; Longenecker et al., 1939; Sporn and Abramovici, 1976; Leclerc et al., 2002; Chadha and Madyastha, 1982; Boutin et al., 1985; Schmitt et al., 2009; Schmitt et al., 2010; Gregiore et al., 2009; Doan et al., 2010; Meyer and Meyer, 1959; Godwin and Michniak, 1997; Ota et al., 2003; Godwin and Michniak, 1999; ECHA REACH Dossier: Nerol; RIFM, 2008d; Horn et al., 2005; Horn et al., 2004; RIFM, 2008b; Rao et al., 2002; Hanley et al., 1999; Hanley et al., 1997; Desiderio et al., 2004; Fliesler and Keller, 1995; Westfall et al., 1997; Crick et al., 1995; Johnson and Shah, 1985; Elliott and Lachance, 1980; DeBarber et al., 2004; Staines et al., 2004; Bobin et al., 1997; RIFM, 2010c; RIFM, 2003a,b,c,d; Strubelt et al., 1999; RIFM, 2010b; Leroy, 1984; Steinberg et al., 1966; Mackie et al., 2009; Atshaves et al., 2004; Arnhold et al., 2002; Fort et al., 1999; Fell et al., 1962; Bernhard et al., 1967; Hidiroglou and Jenkins, 1972; Baxter et al., 1967; Mize et al., 1969; Morin and Srikantaiah, 1982; Gloerich et al., 2005; Steinberg et al., 1965; Krywawych et al., 1985; Gaunt et al., 1969; ECHA REACH Dossier: *cis*-Hex-3-en-1-ol; Dawson et al., 1990.

Literature Search and Risk Assessment Completed On: 02/14/2017.

10.1.3. Developmental and Reproductive Toxicity

The margin of exposure for *trans*-2-hexenol is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on *trans*-2-hexenol or any read-across materials. The total systemic exposure to *trans*-2-hexenol 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 *trans*-2-hexenol. Read-across material, 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section V) has an OECD 414 gavage developmental toxicity study conducted in female Wistar rats. 3-Methyl-2-buten-1-ol was administered via gavage at doses of 0, 50, 200, or 600 mg/kg bw/day on days 6–19 post coitum (PC). The NOAEL was determined to be 600 mg/kg/day for developmental toxicity endpoint, the highest dosage tested (RIFM, 2002a,b). Therefore, the *trans*-2-hexenol MOE for the developmental toxicity endpoint can be calculated by dividing the 3-methyl-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to *trans*-2-hexenol, 600/0.00071 or 845070.

In addition, the total systemic exposure to *trans*-2-hexenol (0.71 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on *trans*-2-hexenol. Read-across material 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section V) has an enhanced OECD 408 oral (drinking water) 90-day subchronic toxicity study conducted in rats. Groups of 10 rats/sex/dose were administered 3-methyl-2-buten-1-ol in drinking water at concentrations of 0, 200, 1000, or 5000 ppm for 90 days (equivalent to 0, 14.4, 65.4, or 243.8 mg/kg/day for males and 0, 21.0, 82.1, or 307.2 mg/kg/day for females, respectively). The study was conducted according to the OECD 408 guideline. There were no effects on sperm parameters up to the highest dose of 5000 ppm or 243.8 mg/kg/day for males (RIFM, 2002a,b). However, the female estrous cycling was not monitored. Hence, a NOAEL could not be derived for the female reproductive toxicity endpoint. The total systemic exposure to *trans*-2-hexenol (0.71 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2010a,d; Hagan et al., 1967; Bar and Griepentrog, 1967; RIFM, 2010e,f; Gilpin et al., 2010; RIFM, 2008a,c; RIFM, 2001; RIFM, 1954; Vieira et al., 2011; Fielden et al., 2007; Hood et al., 1978; Abramovici and Feder, 1980; Abramovici, 1972; Forschmidt et al., 1979; Abramovici and Rachmuth-Roizman, 1983; Howes et al., 2002; Buchbauer et al., 1993; Chadha and Madyastha, 1984; King and Dickinson, 2000; King and Dickenson, 2003; Westfall et al., 1997; Piccinini, 1962; Longenecker et al., 1939; Sporn and Abramovici, 1976; Leclerc et al., 2002; Chadha and Madyastha, 1982; Boutin et al., 1985; Schmitt et al., 2009; Schmitt et al., 2010; Gregiore et al., 2009; Doan et al., 2010; Meyer and Meyer, 1959; Godwin and Michniak, 1997; Ota et al., 2003; Godwin and Michniak, 1999; ECHA REACH Dossier: Nerol; RIFM, 2008d; Horn et al., 2005; Horn et al., 2004; RIFM, 2008b; Rao et al., 2002; Hanley et al., 1999; Hanley et al., 1997; Desiderio et al., 2004; Fliesler and Keller, 1995; Westfall et al., 1997; Crick et al., 1995; Johnson and Shah, 1985; Elliott and Lachance, 1980; DeBarber et al., 2004; Staines et al., 2004; Bobin et al., 1997; RIFM, 2010c; RIFM, 2003a,b,c,d; Strubelt et al., 1999; RIFM, 2010a; Leroy, 1984; Steinberg et al., 1966; Mackie et al., 2009; Atshaves et al., 2004; Arnhold et al., 2002; Fort et al., 1999; Fell et al., 1962; Bernhard et al., 1967; Hidiroglou and Jenkins, 1972; Baxter et al., 1967; Mize et al., 1969; Morin and Srikantaiah, 1982; Gloerich et al., 2005; Steinberg et al., 1965; Krywawych et al., 1985; Gaunt et al., 1969; ECHA REACH Dossier: *cis*-Hex-3-en-1-ol; Dawson et al., 1990.

Literature Search and Risk Assessment Completed On: 11/28/2016.

10.1.4. Skin sensitization

Based on the existing data and application of DST, *trans*-2-hexenol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment

Based on the application of DST, *trans*-2-hexenol 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 2.6.6.; OECD toolbox v3.3). However, a local lymph node assay (LLNA) reported *trans*-2-hexenol as a weak sensitizer with a calculated EC3 value of 60% or 15000 μg/cm^2. A confirmatory human maximization test on 25 subjects with 4% or 2760 μg/cm^2 *trans*-2-hexenol in petrolatum did not result in sensitization reactions in any of the subjects tested. Due to limited data, the current exposure is benchmarked against the non-reactive DST of 900 μg/cm^2. The 95th percentile dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories. trans-2-Hexenol does not present a concern for skin sensitization (Table 1).

Additional References: Natsch et al., 2007; McKim et al., 2010.

Table 1
Acceptable exposure limits for *trans*-2-hexenol based on DST non-reactive.

IFRA Category[a]	Examples of Product Type	Calculated QRA
1	Lip Products	0.026%
2	Deodorant/Antiperspirant	0.033%
3	Hydroalc., Shaved Skin	0.136%
4	Hydroalc., Unshaved Skin	0.407%
5	Women Facial Cream	0.214%
6	Mouthwash	0.652%
7	Intimate Wipes	0.068%
8	Hair Styling Aids Non-Spray	0.91%
9	Conditioners, Rinse-off	4.50%
10	Hard Surface Cleaners	2.5%
11	Candle (Non-Skin/Incidental Skin)	Not Restricted

Note: [a]For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc/QRAInfoJuly2011.pdf).

Literature Search and Risk Assessment Completed On: 09/23/16.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, *trans*-2-hexenol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment

There are no predictive studies available on *trans*-2-hexenol in experimental models. The available UV/Vis spectra for *trans*-2-hexenol indicate no significant absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxic effects. Based on the lack of absorbance in the critical range, and benchmark evaluation, *trans*-2-hexenol does not present a concern for phototoxicity or photoallergenicity.

10.1.6. UV spectra analysis

The available UV/Vis spectra for *trans*-2-hexenol indicate no significant absorbance between 290 and 700 nm. Molar absorption coefficient for λ max between 290 and 700 nm is below the benchmark of concern for phototoxicity, 1000 $L\,mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.1.7. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, *trans*-2-hexenol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.7.1. Risk assessment

There are limited inhalation data available on *trans*-2-hexenol. Based on the Creme RIFM Model, the inhalation exposure is 0.0062 mg/day. This exposure is 226 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: Helmig et al., 1999b; Helmig et al., 1999a; Ito et al., 2009.

Literature Search and Risk Assessment Completed On: 9/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *trans*-2-hexenol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening-level 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, *trans*-2-hexenol 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 *trans*-2-hexenol as either being possibly persistent nor 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 current Volume of Use (2011), *trans*-2-hexenol does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.3. Other available data. *trans*-2-Hexenol has been pre-registered for REACH with no additional data 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 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)**	301.1			1,000,000	0.3011	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.6	1.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1[a]	< 1[a]
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

[a] Combined volumes for both CAS numbers.

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

The RIFM PNEC is 0.3011 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 6/2/15.

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.2018.06.033.

Appendix

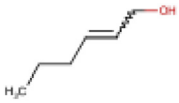
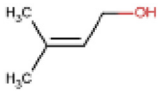
Read-across justification

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, 2012).

- 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, 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	*trans*-2-Hexenol	3-Methyl-2-buten-1-ol
CAS No.	928-95-0	556-82-1
Structure		
Similarity (Tanimoto score)[1]		0.761
Read-across endpoint		• Repeated dose • Developmental & Reproductive
Molecular Formula	$C_6H_{12}O$	$C_5H_{10}O$
Molecular Weight	100.16	86.13
Melting Point (°C, EPI Suite)	−38.47	−59.25
Boiling Point (°C, EPI Suite)	165.73	140
Vapor Pressure (Pa @ 25 °C, EPI Suite)	121	314
Log Kow (KOWWIN v1.68 in EPI Suite)	1.61	1.17
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	15475	75313
J_{max} (mg/cm^2/h, SAM)	508.14	1096.24
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.55E-005	1.38E-005
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non-cyclic	• Non-binder, non-cyclic
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Toxicant (good reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

- 3-Methyl-2-buten-1-ol (CAS # 556-82-1) could be used as structurally similar read-across analog for the target material (Z)-2-penten-1-ol (CAS # 1576-95-0) for the repeated dose, developmental, and reproductive toxicity endpoints.
  - ○ The target substance and the read-across analog are structurally similar and belong to the structural class of alpha-beta unsaturated primaty alcohols.
  - ○ The target substance and the read-across analog have the buten-1-ol fragment common among them.
  - ○ The key difference between the target substance and the read-across analog is that the target is a straight chain alcohol while the read-across is a branched alcohol. This structure difference between the target substance and the read-across analog do not raise additional structural alerts, so the structure differences are not relevant from a toxicological perspective.
  - ○ The target substance and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the buten-1-ol fragment. The differences in the structure which are responsible for Tanimoto score < 1 are not relevent from a toxicological perspective.
  - ○ The target substance and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for repeated dose, developmental, and reproductive toxicity endpoints.
  - ○ According to the QSAR OECD Toolbox (v3.4), structural alerts for repeated dose, developmental, and reproductive toxicity endpoints are consistent between the target substance and the read-across analog. The CAESAR v2.1.6 model predicts the read-across analogs to be toxicant with good reliability and the target to be non-toxicant with low reliability. So according to the CAESAR model, the toxicity profile of the read-across analogs is predicted to be that of higher potency compared to the target material.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - ○ The structural alerts for repeated dose, developmental, and reproductive toxicity endpoints are consistent between the metabolites of the read-across analog and the target substance.
  - ○ The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.

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