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RIFM fragrance ingredient safety assessment, *trans*-2-hexenoic acid, CAS Registry Number 13419-69-7

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] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, 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] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, 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] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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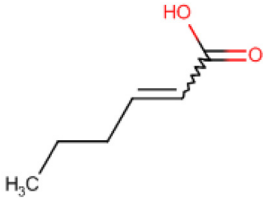
CAS Registry Number: 13419-69-7



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

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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
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-Hexenoic acid was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization potential, and environmental safety. Data show that *trans*-2-hexenoic acid is not genotoxic. The repeated dose toxicity, developmental and reproductive toxicity, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to *trans*-2-hexenoic acid is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; *trans*-2-hexenoic acid is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *trans*-2-hexenoic acid 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, 2016a; RIFM, 2016b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
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: 3.6 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.1 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 229.8 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: 229.8 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.2298 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** *trans*-2-Hexenoic acid
2. **CAS Registry** Number: 13419-69-7
3. **Synonyms:** 2-Hexenoic acid, (E)-; β-Propylacrylic acid; 3-Propylacrylic acid; Hex-2-enoic acid; *trans*-2-Hexenoic acid
4. **Molecular Formula**: $C_6H_{10}O_2$
5. **Molecular Weight**: 114.14
6. **RIFM Number**: 6706

2. Physical data

1. Boiling Point: 92 °C @ 5 mm Hg (FMA), 213.74 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA)
3. **Log K_{ow}:** 1.84 (EPI Suite)
4. **Melting Point**: 25.44 °C (EPI Suite)
5. **Water Solubility:** 7069 mg/L (EPI Suite)
6. **Specific Gravity**: 0.96 (FMA)
7. **Vapor Pressure:** 0.0684 mm Hg @ 20 °C (EPI Suite v4.0), 0.3 mm Hg 20 °C (FMA), 0.115 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: Colorless needle-like crystals; fatty and slightly acrid-musty odor in the pure state; pleasant, fruity-sweet odor in dilution; powerful and comparatively tenacious. In dilutions below 50 ppm, the flavor is pleasant, fruity-warm, somewhat herbaceous, discretely acid. In higher concentrations it shows pungency and less pleasant acid notes.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.000048% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.0000028 mg/kg/day or 0.00020 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.000018 mg/kg/day (RIFM, 2015)

*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 (OECD, 2012)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity**: None
   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**: None

6. Metabolism

Not considered for this risk assessment.

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

trans-2-Hexenoic acids reported to occur in nature in the following foods by the VCF*:

Apple fresh (*Malus* species)
Banana (Musa sapientum L.)
Black currants (*Ribes nigrum* L.)
Citrus Fruits
Guava and Feyoa
Loganberry Juice (*Rubus ursinus* var. *loganobaccus*)
Loquat (*Eriobotrya japonica* Lindl.)
Mentha oils
Peanut (*Arachis hypogaea* L.)
Pork
Starfruit (*Averrhoa carambola* L.)
Tea
Vaccinium species
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

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, *trans*-2-hexenoic acid does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. *trans*-2-Hexenoic acid was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of *trans*-2-hexenoic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method (OECD, 2015). *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *trans*-2-hexenoic acid 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, 2016a). Under the conditions of the study, *trans*-2-hexenoic acid was not mutagenic in the Ames test.

The clastogenic activity of *trans*-2-hexenoic acid was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with *trans*-2-hexenoic acid in DMSO at concentrations up to 1140 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h *trans*-2-Hexenoic acid did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum dose in either non-activated or S9-activated test systems (RIFM, 2016b). Under the conditions of the study, *trans*-2-hexenoic acid was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, *trans*-2-hexenoic acid does not present a concern for genotoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 4/29/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on *trans*-2-hexenoic acid or any read-across materials. The total systemic exposure to *trans*-2-hexenoic acid 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 *trans*-2-hexenoic acid or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to *trans*-2-hexenoic acid (0.018 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: 05/01/2017.

10.1.3. Reproductive and developmental toxicity

There are insufficient reproductive toxicity data on *trans*-2-hexenoic acid or any read-across materials. The total systemic exposure to *trans*-2-hexenoic acid is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

The safety assessment will be updated when exposure data becomes available.

10.1.3.1. Risk assessment. There are no developmental toxicity data on *trans*-2-hexenoic acid or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to *trans*-2-hexenoic acid (0.018 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 *trans*-2-hexenoic acid or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to *trans*-2-hexenoic acid (0.018 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: 05/01/2017.

10.1.4. Skin sensitization

Based on the application of DST, *trans*-2-hexenoic acid does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk Assessment. No skin sensitization studies are available for *trans*-2-hexenoic acid. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13).

No predictive or human confirmatory skin sensitization studies are available for *trans*-2-hexenoic acid. Due to the insufficient data, the reported exposure was compared to the reactive DST of 64 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for *trans*-2-hexenoic acid, which presents no appreciable risk for skin sensitization based on the reactive DST.

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, *trans*-2-hexenoic acid 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 *trans*-2-hexenoic acid 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; Henry et al., 2009). Based on lack of absorbance, *trans*-2-hexenoic acid 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: 04/20/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of

Table 1
Acceptable concentrations for *trans*-2-hexenoic acid based on reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.005	0.000%
2	Products applied to the axillae	0.001	0.00%
3	Products applied to the face using fingertips	0.03	0.000%
4	Fine fragrance products	0.03	0.000%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.01	0.000%[b]
6	Products with oral and lip exposure	0.02	0.000%[b]
7	Products applied to the hair with some hand contact	0.06	0.000%
8	Products with significant ano-genital exposure	0.00	0.000%
9	Products with body and hand exposure, primarily rinse-off	0.05	0.000%[b]
10	Household care products with mostly hand contact	0.19	0.000%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11	0.000%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.004%

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

appropriate data. The material, *trans*-2-hexenoic acid, exposure level 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 *trans*-2-hexenoic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.00020 mg/day. This exposure is 7000 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; 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: 5/8/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *trans*-2-hexenoic acid 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, *trans*-2-hexenoic acid 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-hexenoic acid 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), *trans*-2-hexenoic acid 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. trans-2-Hexenoic acid has been pre-registered for REACH with no data available 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)**	229.8			1,000,000	0.2298	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.8	1.8
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 0.2298 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:** 5/3/17.

11. Literature Search*

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

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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.

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