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Short Review

RIFM fragrance ingredient safety assessment, *n*-hexyl 2-butenoate, CAS Registry Number 19089-92-0

A.M. Api[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], F. Siddiqi[a], 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 Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member 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 Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member 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 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 Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member 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 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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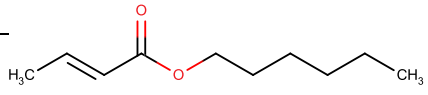

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
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
QSAR - Quantitative Structure-Activity Relationship
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 as 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 existing information supports the use of this material as described in this safety assessment.

n-Hexyl 2-butenoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) show that *n*-hexyl 2-butenoate is not expected to be genotoxic. Data on read-across analog *n*-butyl acrylate (CAS # 141-32-2) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on analog butyl methacrylate (CAS # 97-88-1) provide a calculated MOE > 100 for the reproductive toxicity endpoint. The existing data and analog isobutyl 2-butenoate (CAS # 589-66-2) do not indicate that *n*-hexyl 2-butenoate is a skin sensitizer under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; *n*-hexyl 2-butenoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for Cramer Class I; the exposure to *n*-hexyl 2-butenoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *n*-hexyl 2-butenoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current VoU in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2017; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 147 mg/kg/day.	(ECHA REACH Dossier: Butyl acrylate; ECHA, 2011a)
Reproductive Toxicity: NOAEL = 300 mg/kg/day.	(ECHA REACH Dossier: Butyl methacrylate; ECHA, 2011b)
Skin Sensitization: Data do not indicate skin sensitization at the current, declared levels of use.	RIFM (2013b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 3.26 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 109.5 L/kg (EPI Suite v4.11; US ECHA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 9.31 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: 9.31 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00931 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** *n*-Hexyl 2-butenoate
2. **CAS Registry Number:** 19089-92-0
3. **Synonyms:** 2-Butenoic acid, hexyl ester; Hexyl crotonate; Hexyl but-2-enoate; *n*-Hexyl 2-butenoate
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight:** 170.25
6. **RIFM Number:** 1020
7. **Stereochemistry:** No isomer specified. One geometric center and 2 total geometric isomers possible.

2. Physical data

1. **Boiling Point:** 216.64 °C (EPI Suite)
2. **Flash Point:** 190 °F; CC (FMA)
3. **Log K_{OW}:** 3.6 (EPI Suite)
4. **Melting Point:** −10.31 °C (EPI Suite)
5. **Water Solubility:** 52.1 mg/L (EPI Suite)
6. **Specific Gravity:** 0.889 (FMA)
7. **Vapor Pressure:** 0.103 mm Hg @ 20 °C (EPI Suite v4.0), 0.06 mm Hg 20 °C (FMA), 0.156 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. < 0.1 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.66% (RIFM, 2015)
2. **Inhalation Exposure*:** 0.000031 mg/kg/day or 0.0022 mg/day (RIFM, 2015)
3. **Total Systemic Exposure**:** 0.0073 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, 2015, 2017; and Comiskey et al., 2017).

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7)
   b. **Repeated Dose Toxicity:** Butyl acrylate (*n*-butyl acrylate) (CAS # 141-32-2)
   c. **Reproductive Toxicity:** Butyl methacrylate (CAS # 97-88-1)
   d. **Skin Sensitization:** Isobutyl 2-butenoate (CAS # 589-66-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

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

n-Hexyl 2-butenoate is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species)
Cherimoya (*Annona cherimola* Mill.)
Mountain papaya (*C. candamarcensis, C. pubescens*)
Plum (*Prunus* species)

*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.

9. Reach dossier

n-Hexyl 2-butenoate has been pre-registered for 2010; no dossier available as of 04/29/19.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *n*-hexyl 2-butenoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. *n*-hexyl 2-butenoate was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen HC is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic and clastogenic activity of *n*-hexyl 2-butenoate; however, read-across can be made to ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7; see Section VI). The mutagenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA were treated with ethyl *trans*-2,*cis*-4-decadienoate 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 concentration in the presence or absence of S9 (RIFM, 2017). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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 ethyl *trans*-2,*cis*-4-decadienoate in DMSO at concentrations up to 1960 μg/mL in a DRF study. Micronuclei analysis in the main study was conducted up to 500 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Ethyl *trans*-2,*cis*-4-decadienoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, ethyl *trans*-2,*cis*-4-decadienoate does not present a concern for genotoxic potential, and this can be extended to *n*-hexyl 2-butenoate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/19.

11.1.2. Repeated dose toxicity

The MOE for *n*-hexyl 2-butenoate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *n*-hexyl 2-butenoate. Read-across material butyl acrylate (*n*-butyl acrylate) (CAS # 141-32-2; see Section VI) has sufficient repeated dose toxicity data. In a non-GLP, 90-day, whole-body inhalation toxicity study, *n*-butyl acrylate was administered to 20 Sprague Dawley rats/sex/dose at doses of 0, 21, 108, 211, and 546 ppm for 6 h/day, 5 days/week for 13 weeks (a total of 63 exposures). The doses were equivalent to 0, 29, 147, 286, 741 mg/kg/day using standard minute volume (MV) and body weight (bw) parameters for Sprague Dawley rats. At 211 ppm, the test material caused irritation of the eye and nasal mucosa. Significant reductions in body weight changes were observed in both sexes. Alterations in female clinical chemistry included a decrease in potassium levels and an increase in ALP activity at the 211 ppm dose (286 mg/kg/day). Approximately 77% (31/40) mortality was reported in animals of the high-dose group. Hemorrhagic discharge from the eyes and nose combined with severe dyspnea were observed, and the severity of effects increased constantly with dose and treatment duration. In addition, several clinical chemistry and hematological parameters were affected in high-dose group animals. Metaplasia of the respiratory epithelium as far as the terminal bronchioles and proliferation of the bronchoalveolar epithelium were detected in both sexes at the highest dose during histopathological examinations. Overall, the NOAEL for systemic toxicity was considered to be 147 mg/kg/day based on incidences of mortality among the high- and mid-dose group animals (ECHA, 2011a).

In another study conducted with *n*-butyl acrylate administered to rats for 2-years showed that *n*-butyl acrylate showed no indications of systemic toxicity or tumorigenic activity. Furthermore, the study has been reviewed by IARC, which concluded that *n*-butyl acrylate is non-carcinogenic (group 3) at doses up to 184 mg/kg/day (ECHA, 2011a). Similarly, lifetime dermal application of 1% *n*-butyl acrylate did not demonstrate any indications of tumor formation (ECHA, 2011a).

In another study, a GLP-compliant subchronic toxicity study, groups of 15 Fischer 344 rats/sex/dose were administered concentrations of 0%, 0.015%, 0.09%, 0.15% *n*-butyl acrylate in drinking water for 90 days (equivalent doses 0, 12, 73, 84 mg/kg/day in males and 0, 15, 91, 111 mg/kg/day in females). No treatment-related effects were reported among treated animals. In a follow-up study, conducted with 5 Fischer 344 rats/sex administered *n*-butyl acrylate via gavage at 150 mg/kg/day for 96–97 days, no signs of toxic effects were reported. Thus, the NOAEL for this study was considered to be 150 mg/kg/day (ECHA, 2011a). The results of this study are in close agreement to the NOAEL of 147 mg/kg/d, described above, which is considered the NOAEL for this safety assessment.

Therefore, the *n*-hexyl 2-butenoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the *n*-butyl acrylate NOAEL in mg/kg/day by the total systemic exposure to *n*-hexyl 2-butenoate, 147/0.0073, or 20137.

In addition, the total systemic exposure to *n*-hexyl 2-butenoate (7.3 μg/kg/day) is below the TTC (30 μg/kg/day; RIFM, 1985a) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/19.

11.1.3. Reproductive toxicity

The MOE for *n*-hexyl 2-butenoate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on *n*-hexyl 2-butenoate. Read-across material butyl methacrylate (CAS # 97-88-1; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint.

In an OECD 414/GLP prenatal developmental toxicity study, Himalayan time-mated female rabbits (25 females/dose) were orally (via stomach tube) administered *n*-butyl methacrylate at doses of 0 (1% carboxymethylcellulose suspension in drinking water, a few drops of Cremophor EL, and one drop of hydrochloric acid), 100, 300, and 1000 mg/kg/day on gestation days (GDs) 6 through 28. Does were euthanized at GD 29. A total of 7 high-dose treated does were euthanized due to abortion on GDs 24–28. There were significant reductions in food consumption and body weights of mid- and high-dose females. The mean gravid uterus weight was significantly reduced among high-dose females. At necropsy, stomach erosion, no feces in the small intestine, and watery feces in the intestine were observed among high-dose females. These findings were related to significantly reduced food consumption and were considered to be treatment-related. A complete post-implantation loss in 2 individual does secondary to

distinct maternal toxicity were observed at the highest dose. Significant reductions in fetal weights were observed at the highest dose. Slightly but significantly higher incidences of malformation (mainly severely-fused sternebrae) and skeletal variations (delayed ossification and supernumerary ribs, commonly associated with decreased fetal weight and maternal stress) were observed at the highest dose. Therefore, mean fetal malformations and variations were also significantly higher in the high-dose group as compared to the control. No treatment-related developmental effects were observed among animals of the low and mid-dose groups. Therefore, the NOAEL for maternal toxicity was considered to be 100 mg/kg/day, based on reduced food consumption and bodyweight gain observed at doses ≥300 mg/kg/day. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, based on abortions, decreased fetal growth and skeletal alterations observed at 1000 mg/kg/day (ECHA, 2011b).

In another study, female Sprague Dawley rats (22–25/dose) were exposed via inhalation (whole-body) to *n*-butyl methacrylate at doses of 0 (filtered air), 100, 300, 600, and 1200 ppm (analytical concentrations 0, 99.6 ± 5.0, 301.6 ± 12.2, 602.3 ± 38.0, and 1206.4 ± 46.9 ppm, equivalent to 0, 600, 1800, 3600, or 7200 mg/m^3) for 6 h/day, during GDs 6 to 20. Dams were euthanized on GD 21. No treatment-related mortality was observed. The maternal bodyweight gains significantly decreased during the first half (GD 6–13) of the treatment at doses of 300 ppm and above. Furthermore, overall bodyweight gain was significantly reduced among high-dose animals throughout GDs 6–21. A statistically significant reduction in maternal food consumption was observed at doses 300 ppm (during GDs 6–13) and 1200 ppm (during GDs 6–13 and GDs 6–21). Fetal body weights significantly decreased at 600 ppm in females and at 1200 ppm in both sexes. A statistically significant increase in the mean percentage of fetuses with skeletal variations (mainly including incomplete ossification of sternebrae and thoracic vertebral centra) was observed at 1200 ppm, compared to controls. The author stated that the biological relevance of these findings was limited because the observed incidences occurred with no clear dose-response. It was concluded that these findings were suggestive of slight fetotoxicity. Therefore, the NOAEC for maternal toxicity was considered to be 100 ppm (600 mg/m^3 or 183 mg/kg/day), based on significantly reduced body weight at higher doses. The NOAEC for developmental toxicity was considered to be 300 ppm (1800 mg/m^3 or 550 mg/kg/day), based on significantly reduced fetal body weights at higher doses (Saillenfait et al., 1999; also included in ECHA, 2011b).

In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening study, Crj:CD(SD) rats (10/sex/dose) were gavaged *n*-butyl methacrylate at doses of 0 (vehicle - Sesame oil), 30, 100, 300, and 1000 mg/kg/day for 44 days in males (a total period of before, during and after mating), and 14 days before mating and up to day 3 of lactation in females. No treatment-related effects were observed on the reproductive performance, reproductive function (estrous cyclicity and sperm parameters), and reproductive organs of males and females treated up to 1000 mg/kg/day. There were no treatment-related effects on gestation index, gestation length, or the number of pups per litter. Furthermore, offspring viability and sex ratio of pups were unaffected due to treatment. Significant decreases in the number of corpora lutea and implantation sites were observed in dams treated at 1000 mg/kg/day. However, necropsy examination revealed no alterations in the implantation rate and anomalies of follicle formation in the ovary. Hence, the author considered that the decrease in the number of corpus lutea or implantation sites were due to abnormal ovulation. Furthermore, there were no effects on birth rate, gestation length, and nursing condition. Therefore, the NOAEL for fertility was considered to be 1000 mg/kg/day for males, the highest tested dose, and 300 mg/kg/day for females, based on the decreased number of corpus lutea or implantation. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest tested dose (ECHA, 2011b).

The most conservative NOAEL for reproductive toxicity (developmental toxicity and fertility) was considered to be 300 mg/kg/day, based on the gavage developmental toxicity study in rabbits and the OECD 422 gavage study in rats.

Therefore, the *n*-hexyl 2-butenoate MOE for the reproductive toxicity endpoint can be calculated by dividing the butyl methacrylate NOAEL in mg/kg/day by the total systemic exposure to *n*-hexyl 2-butenoate, 300/0.0073 or 41096.

In addition, the total systemic exposure to *n*-hexyl 2-butenoate (7.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007a; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/27/19.

11.1.4. Skin sensitization

The existing data and read-across material isobutyl 2-butenoate (CAS # 589-66-2) do not indicate that *n*-hexyl 2-butenoate is a skin sensitizer under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for *n*-hexyl 2-butenoate. Existing data and read-across material isobutyl 2-butenoate (CAS # 589-66-2; see Section VI), do not indicate that *n*-hexyl 2-butenoate is a skin sensitizer under the current, declared levels of use. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a human maximization test, no skin sensitization reactions were observed with *n*-hexyl 2-butenoate at 10% or 6900 μg/cm^2 (RIFM, 1977). Additionally, in 2 confirmatory human repeat insult patch tests (HRIPT) with 3.8% (2094 μg/cm^2) in 1:3 ethanol:diethyl phthalate or 2.5% (1938 μg/cm^2) in alcohol SDA 39C of read-across material isobutyl 2-butenoate, no reactions indicative of sensitization were observed in any of the 105 and 38 volunteers, respectively (RIFM, 2013b; RIFM, 1971).

Based on WoE from structural analysis, human studies, and read-across material isobutyl 2-butenoate, data do not indicate that *n*-hexyl 2-butenoate is a skin sensitizer under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/16/19.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *n*-hexyl 2-butenoate 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 the lack of absorbance, *n*-hexyl 2-butenoate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/03/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *n*-hexyl 2-butenoate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on *n*-hexyl 2-butenoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0022 mg/day. This exposure is 636.4 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: 04/08/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *n*-hexyl 2-butenoate 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, *n*-hexyl 2-butenoate 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 v4.11 (US ECHA, 2012a) did not identify *n*-hexyl 2-butenoate as being 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 v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment Section prior to Section 1.

11.2.2. Risk assessment

Based on current VoU (2015), *n*-hexyl 2-butenoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

n-Hexyl 2-butenoate has been pre-registered for REACH with no additional data at this time.

11.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are highlighted.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	9.31			1000000	0.00931	

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

Exposure	Europe	North America
Log K_{ow} Used	3.6	3.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	NA
Risk Characterization: PEC/PNEC	**< 1**	**NA**

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

The RIFM PNEC is 0.00931 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/02/19.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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. The links listed above were active as of 09/30/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111224.

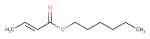
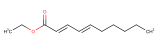
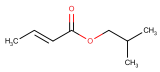
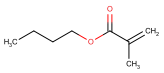
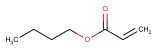
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 Chemicals 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US ECHA, 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	*n*-Hexyl 2-butenoate	Ethyl *trans*-2,*cis*-4-decadienoate	Isobutyl 2-butenoate	Butyl methacrylate	Butyl acrylate
CAS No.	19089-92-0	3025-30-7	589-66-2	97-88-1	141-32-2
Structure					
Similarity (Tanimoto Score)		0.44	0.65	0.60	0.71
Read-across Endpoint		• Genotoxicity	• Skin Sensitization	• Reproductive Toxicity	• Repeated Dose Toxicity
Molecular Formula	$C_{10}H_{18}O_2$	$C_{12}H_{20}O_2$	$C_8H_{14}O_2$	$C_8H_{14}O_2$	$C_7H_{12}O_2$
Molecular Weight	170.25	196.29	142.19	142.19	128.17
Melting Point (°C, EPI Suite)	−10.31	10.62	−44.52	−75	−64.6
Boiling Point (°C, EPI Suite)	216.64	258.41	163.76	160	145
Vapor Pressure (Pa @ 25 °C, EPI Suite)	20.80	2.31	280	283	7.27E+002
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.60	4.36	2.54	2.88	2.36
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	52.1	8.588	555.2	800	902.1
J_{max} (μg/cm^2/h, SAM)	37.150	3.248	193.182	68.764	55.348
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.05E+001	7.64E+001	3.44E+001	5.03E+001	4.66E+001
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found			
DNA Binding (OECD QSAR Toolbox v4.2)	• Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α, β−unsaturated esters	• Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α, β−unsaturated esters			
Carcinogenicity (ISS)	• No alert found	• No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found			
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found			
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found			
Oncologic Classification	• Acrylate Reactive Functional Groups	• Acrylate Reactive Functional Groups			
Repeated Dose Toxicity					
Repeated Dose (HESS)	• Not categorized				• Not categorized
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure			• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v-2.1.6)	• Non-toxicant (low reliability)			• Toxicant (low reliability)	
Skin Sensitization					
Protein Binding (OASIS v1.1)	• Michael addition|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-carbonyl compounds with polarized double bonds		• Michael addition|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-carbonyl compounds with polarized double bonds		

Protein Binding (OECD)	• Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters		• Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters		
Protein Binding Potency	• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkyl 2-alkenoates (MA)		• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkyl 2-alkenoates (MA)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Michael Addition|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-carbonyl compounds with polarized double bonds		• Michael Addition|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-carbonyl compounds with polarized double bonds		
Skin Sensitization Reactivity Domains (Toxtree v-2.6.13)	• Alert for Michael acceptor		• Alert for Michael acceptor		
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• See Supplemental Data 4	• See Supplemental Data 5

Summary

There are insufficient toxicity data on *n*-hexyl 2-butenoate (CAS # 19089-92-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7), isobutyl 2-butenoate (CAS # 589-66-2), butyl methacrylate (CAS # 97-88-1), and butyl acrylate (CAS # 141-32-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) was used as a read-across analog for the target material *n*-hexyl 2-butenoate (CAS # 19089-92-0) for the genotoxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of linear α,β-unsaturated esters.
  - ○ The target material and the read-across analog share linear alkyl alcohol ester structures.
  - ○ The key difference between the target material and the read-across analog is that the target material has a linear α,β-unsaturated C4 acid branch and a linear C6 saturated alcohol branch, whereas the read-across analog has a linear α,β,γ-unsaturated C10 acid branch with unsaturations at positions 2 and 4 and a C2 saturated alcohol branch. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While percentage skin absorption estimated from J_{max} indicates exposure to the material, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ Because both the target material and the read-across analog are α,β-unsaturated esters, they are predicted to have Michael addition DNA binding alerts by OECD for genotoxicity. Furthermore, they have an oncologic alert for acrylate reactive functional groups, but both the target material and the read-across analog are longer chain unsaturated esters that lack the reactivity of acrylates. Thus, the alerts for the target material and read-across analog are comparable. The data described in the genotoxicity section above show that the read-across analog does not pose a concern for the genotoxicity endpoint. The predictions are superseded by the data.
  - ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Isobutyl 2-butenoate (CAS # 589-66-2) was used as a read-across analog for the target material *n*-hexyl 2-butenoate (CAS # 19089-92-0) for the skin sensitization endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated esters.
  - ○ The target material and the read-across analog share an α,β-butenoic acid branch.
  - ○ The key difference between the target material and the read-across analog is that the target material has a linear C6 saturated alcohol whereas

the read-across analog has a branched isobutanol saturated alcohol. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are predicted to have protein binding alerts by OASIS and OECD characterization schemes for skin sensitization. In addition, they are also predicted to have alerts for reactivity domains by Toxtree and are classified as moderately reactive. This shows that the alerts for the target material and read-across analog are comparable. The data described in the skin sensitization section above shows that the read-across analog does not pose a concern for the skin sensitization endpoint. Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Butyl methacrylate (CAS # 97-88-1) was used as a read-across analog for the target material *n*-hexyl 2-butenoate (CAS # 19089-92-0) for the reproductive toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated esters.
  - The target material and the read-across analog share an α,β-unsaturated acid branch and an alkyl linear saturated alcohol branch.
  - The key difference between the target material and the read-across analog is that the target material has a linear α,β-unsaturated C4 acid moiety and a linear C6 saturated alcohol group whereas, the read-across analog has a branched α,β-unsaturated methacrylic acid and a C4 saturated alcohol group. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity, while the target material is predicted to be a non-toxicant. The data described in the developmental toxicity section above shows that the read-across analog has an adequate MOE at the current level of use. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Butyl acrylate (CAS # 141-32-2) was used as a read-across analog for the target material *n*-hexyl 2-butenoate (CAS # 19089-92-0) for the repeated dose toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated esters.
  - The target material and the read-across analog share an α,β-unsaturated acid branch and a saturated linear alcohol branch.
  - The key difference between the target material and the read-across analog is that the target material has a linear C6 saturated alcohol and a C4 α,β-unsaturated acid moiety, whereas, the read-across analog has a linear C4 saturated alcohol and a C3 α,β-unsaturated acid moiety. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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