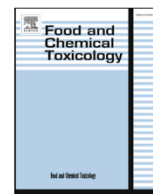




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Short Review

RIFM fragrance ingredient safety assessment, hexyl isobutyrate, CAS Registry Number 2349-07-7



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. Lieblerⁱ, 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, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö, SE, 20502, Sweden

^d Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, 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 Würzburg, 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 of 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

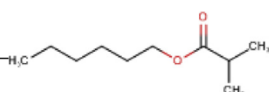
^k Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^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

Version: 050619. This version replaces any previous versions.

Name: Hexyl isobutyrate
CAS Registry Number: 2349-07-7

**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

* Corresponding author.

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

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Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.

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

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 48-h Algae EC50: 1.24-2 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.1242 µg/L

Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

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.

Hexyl isobutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that hexyl isobutyrate is not genotoxic. Data on read-across propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog hexyl 2-methylbutyrate (CAS # 10032-15-2) do not indicate that hexyl isobutyrate is a sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; hexyl isobutyrate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to hexyl isobutyrate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; hexyl isobutyrate was found not to be PBT as per the 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, 2003; RIFM, 2014)

Repeated Dose Toxicity: NOAEL = 50 mg/kg/day. ((RIFM, 2002)

Reproductive Toxicity: Developmental toxicity: NOAEL = 250 mg/kg/day. Fertility: 1000 mg/kg/day. (RIFM (2009)

Skin Sensitization: Data do not indicate hexyl isobutyrate is a skin sensitizer. (RIFM (2018)

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:Critical Measured Value: 76% (OECD 3-01F) (RIFM (1998b)

Bioaccumulation:Screening-level: 135.8 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:Screening-level: 48-h Algae EC50: 1.24-2 mg/L (ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

1. Identification

- 1. Chemical Name:** Hexyl isobutyrate
- 2. CAS Registry Number:** 2349-07-7
- 3. Synonyms:** Hexyl 2-methylpropanoate; Propanoic acid, 2-methyl-, hexyl ester; Hexyl-n Isobutyrate; 7' 烷酸アルキル(C = 1~7); Hexyl isobutyrate
- 4. Molecular Formula:** C₁₀H₂₀O₂
- 5. Molecular Weight:** 172.26
- 6. RIFM Number:** 976
- 7. Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

- 1. Boiling Point:** 199 °C (FMA), 198.83 °C (EPI Suite)
- 2. Flash Point:** 73 °C (GHS), 169 °F; CC (RIFM Database)
- 3. Log K_{OW}:** Log Pow = 4.6 (RIFM, 1998a), 3.74 (EPI Suite)
- 4. Melting Point:** -20.47 °C (EPI Suite)
- 5. Water Solubility:** 38.59 mg/L (EPI Suite)
- 6. Specific Gravity:** Not Available
- 7. Vapor Pressure:** 0.259 mm Hg @ 20 °C (EPI Suite v4.0), 0.2 mm Hg @ 20 °C (FMA), 0.382 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 liquid. Powerful, but rather harsh-fruity, nondescript type of odor

3. Volume of use (worldwide band)

- 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

- 1. 95th Percentile Concentration in Hydroalcohols:** 0.032% (RIFM, 2019)
- 2. Inhalation Exposure*:** 0.00042 mg/kg/day or 0.030 mg/day (RIFM, 2019)
- 3. Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2019)

*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 5. 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).

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 v 3.1.0	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:

- Genotoxicity:** None
 - Repeated Dose Toxicity:** Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1)
 - Reproductive Toxicity:** Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1)
 - Skin Sensitization:** Hexyl 2-methylbutyrate (CAS # 10032-15-2)
 - Phototoxicity/Photoallergenicity:** None
 - Local Respiratory Toxicity:** None
 - Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

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

Hexyl isobutyrate is reported to occur in the following foods by the VCF*:

- Apple fresh (*Malus* species).
- Apple processed (*Malus* species).
- Apricot (*Prunus armeniaca* L.)
- Chinese quince (*Pseudocarya sinensis* Schneid).
- Grape (*Vitis* species).
- Hop (*Humulus lupulus*).
- Mentha oils.
- Spineless monkey orange (*Strychnos madagasc.*)
- Wine.
- Wormwood oil (*Artemisia absinthium* L.)

*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

Available; accessed 05/06/19.

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 current existing data, hexyl isobutyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Hexyl isobutyrate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity at the highest concentration tested (861 µg/mL) with and without metabolic activation (RIFM, 2015a). BlueScreen HC is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of hexyl isobutyrate 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with hexyl isobutyrate in ethanol (EtOH) 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, 2003). Under the conditions of the study, hexyl isobutyrate was not mutagenic in the Ames test.

The clastogenic activity of hexyl isobutyrate 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 hexyl isobutyrate in EtOH at concentrations up to 1720 µg/mL in the DRF study. Micronuclei analysis was conducted at concentrations up to 400 µg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Hexyl isobutyrate 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, 2014). Under the conditions of the study, hexyl isobutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, hexyl isobutyrate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/11/19.

11.1.2. repeated dose toxicity

The MOE 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 hexyl isobutyrate. Read-across material propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1; see Section 6) has sufficient repeated dose toxicity data. In an OECD 407 and GLP-compliant subchronic study, 5 Sprague Dawley rats/sex/group were administered propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate through gavage at doses of 0, 15, 150 and 1000 mg/kg/day. No treatment-related adverse effects were observed in the low- and mid-dose groups. In the high-dose group, transient salivation was observed during the study starting on study day 3. In addition, significant decreases were reported in reduced erythrocyte count and mean corpuscular hemoglobin concentration and increases in mean corpuscular volume were also reported. These hematological alterations were associated with mild macrocytic anemia potentially of hemolytic origin. Furthermore, liver hypertrophy was reported in animals of both sexes. The hypertrophy was characterized by increased absolute and relative liver weights as well as centrilobular hepatocyte enlargement and mononuclear cell foci. Thus, based on treatment-related alterations of hematology and the liver observed in animals of both sexes in the highest-dose group, the NOAEL for repeated dose toxicity endpoint was considered to be 150 mg/kg/day (RIFM, 2002).

A default safety factor of 3 was applied as the above NOAEL is from the 28-day OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 150/3 or 50 mg/kg/day.

Therefore, the hexyl isobutyrate MOE for the repeated dose toxicity

endpoint can be calculated by dividing the NOAEL of propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate in mg/kg/day by the total systemic exposure to hexyl isobutyrate, 50/0.0013 or 38462.

In addition, the total systemic exposure to hexyl isobutyrate (1.3 µg/kg/day) is below the TTC (30 µg/kg/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/19.

11.1.3. Reproductive toxicity

The MOE for hexyl isobutyrate 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 hexyl isobutyrate. Read-across material propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1; see Section 6) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD 416/GLP 2-generation reproduction study was conducted in Sprague Dawley rats. Groups of 28 rats/sex/dose (F0) and 24 rats/sex/dose (F1) were administered propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate via oral gavage at doses of 0, 50, 250, or 1000 mg/kg/day in Arachis oil for at least 10 weeks. F0 and F1 animals were administered their respective doses from study day 1 and day 21 of age, respectively, up to the pairing period for males and up to the pairing and lactation periods for females. No treatment-related mortality and clinical signs were observed in any of the animals from either generation. Transient salivation was observed post-dosing in both generations at 250 and 1000 mg/kg/day in the initial weeks of treatment, which was attributed to the palatability of the test material. No treatment-related changes were observed in body weight and food consumption of animals of either generation when compared to their respective control groups. No treatment-related changes were observed for estrous cycles, mating, pregnancy and partition indices, and number of corpora lutea and implantations at all dose levels in both generations. No treatment-related adverse effects were observed in sperm assessments (sperm concentration, motility, progressive motility, morphology, and spermatid count) for males in both generations. Cortical vacuolation, testicular atrophy (males), reduced seminal vesicle content (males), prostate interstitial inflammation cell infiltrates (males), and uterus (females: focal hemorrhage, fibrosis, foam cell accumulation, and hemosiderin pigment deposition) were observed in both generation animals at all doses including the controls, and thus, were considered to be common background microscopic observations. At 1000 mg/kg/day, there was a decrease in litter size at birth and on day 1, and the survival rate was less than the control group for both generations. Litter weight at 1000 mg/kg/day in both generations was statistically significantly reduced when compared to controls, which was attributed to the secondary effects of decreased litter size at this dose. Furthermore, delays in incisor eruption in F1 and F2 offspring and late pinna unfolding in F2 offspring were observed at 1000 mg/kg/day. Age at eye opening, day 1 anogenital distance (F2 offspring only), percentage of offspring with successful reflexological assessments, and age of sexual maturity were not affected by treatment in both generations and did not indicate any disturbance in the development of offspring. Specific organ toxicity included significantly increased liver and kidney weights (high-dose F0 and F1 only), enlarged liver (high-dose F1 only), and microscopic alterations in the liver (all dose groups including controls for both F0 animals and F1 males). These hepatic changes were considered to be attributed to the administration of xenobiotics, and hence, not considered to be toxicologically significant. The NOAEL for fertility effects was considered to be 1000 mg/kg/day, the highest dose

tested. The NOAEL for developmental toxicity was considered to be 250 mg/kg/day, based on delays in developmental landmarks (incisor eruption and pinna unfolding) and decreased litter size among high-dose group offspring (RIFM, 2009; ECHA, 2012b).

The hexyl isobutyrate MOE for the developmental toxicity endpoint can be calculated by dividing the propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate NOAEL in mg/kg/day by the total systemic exposure to hexyl isobutyrate, 250/0.0013 or 192308.

The hexyl isobutyrate MOE for the fertility endpoint can be calculated by dividing the propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate NOAEL in mg/kg/day by the total systemic exposure to hexyl isobutyrate, 1000/0.0013 or 769231.

In addition, the total systemic exposure to hexyl isobutyrate (1.3 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007; 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: 06/11/19.

11.1.4. Skin sensitization

Data on read-across material hexyl 2-methylbutyrate (CAS # 10032-15-2) do not indicate hexyl isobutyrate is a skin sensitizer.

11.1.4.1. Risk assessment. Insufficient data are available on hexyl isobutyrate. Based on existing data and data on read-across material hexyl 2-methylbutyrate (CAS # 10032-15-2; see Section 6) do not indicate hexyl isobutyrate is a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree 3.1.0). Read-across material hexyl 2-methylbutyrate was found to be negative in an *in chemico* direct peptide reactivity assay (DPRA) and *in vitro* KeratinoSens (RIFM, 2015b). Furthermore, in a guinea pig open epicutaneous test (OET), read-across material hexyl 2-methylbutyrate did not present reactions indicative of sensitization (Klecak, 1985). In human maximization tests, no skin sensitization reactions were observed with 4% hexyl isobutyrate or 10% read-across material hexyl 2-methylbutyrate in petrolatum (RIFM, 1977b; RIFM, 1977a). In a confirmatory human repeat insult patch test (HRIPT), hexyl isobutyrate did not induce sensitization reactions at 0.25% or 193 µg/cm² (RIFM, 1965). Additionally, in HRIPTs with 7086 µg/cm² (in 3:1 DEP:EtOH) or 967 µg/cm² of read-across material hexyl 2-methylbutyrate (in alcohol SDA 39C), no reactions indicative of sensitization was observed in any of the 109 or 38 volunteers, respectively (RIFM, 2018; RIFM, 1972).

Based on weight of evidence from structural analysis and *in vitro* animal and human studies on read-across material hexyl 2-methylbutyrate, data do not indicate hexyl isobutyrate is a skin sensitizer.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/14/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hexyl isobutyrate 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 hexyl isobutyrate 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, hexyl isobutyrate 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, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/19.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on hexyl isobutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.030 mg/day. This exposure is 46.7 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: 06/21/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of hexyl isobutyrate 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, hexyl isobutyrate was identified as a fragrance material with the 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 EPA, 2012a) did not identify hexyl isobutyrate 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, 2012a). For persistence, if the EPI Suite model BOWIN 3 predicts a value < 2.2 and either BOWIN 2 or BOWIN 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 $\geq 2000 \text{ L/kg}$. 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 BOWIN 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 the current Volume of Use (2015), hexyl isobutyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 1998b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 76% was observed after 28 days.

11.2.3.2. Ecotoxicity. No data available.

11.2.3.3. Other available data. Hexyl isobutyrate has been registered for REACH with no additional data at this time.

11.2.3.4. Risk assessment refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>1.270</u>			1000000	0.00127	
ECOSAR Acute Endpoints (Tier 2) v1.11	2.227	3.844	<u>1.242</u>	10000	0.1242	Esters
ECOSAR Acute Endpoints (Tier 2) v1.11	3.895	2.597	3.754			Neutral Organic SAR

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

Exposure	Europe	North America
Log K_{ow} Used	4.6	4.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is 0.1242 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/14/19.

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/opthpv/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/>

12.1. 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.2020.111196>.

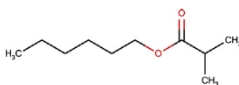
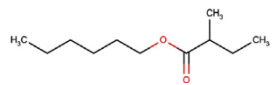
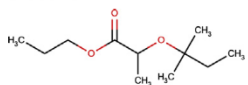
Appendix

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 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 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
Principal Name	Hexyl isobutyrate	Hexyl 2-methylbutyrate	Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate
CAS No.	2349-07-7	10032-15-2	319002-92-1
Structure			
Similarity (Tanimoto Score)		0.94	0.41
Read-across Endpoint		<ul style="list-style-type: none"> • Skin Sensitization 	<ul style="list-style-type: none"> • Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_{10}H_{20}O_2$	$C_{11}H_{22}O_2$	$C_{11}H_{22}O_3$
Molecular Weight	172.268	186.295	202.294
Melting Point (°C, EPI Suite)	-20.47	-9.14	3.41
Boiling Point (°C, EPI Suite)	198.83	218.34	219.10
Vapor Pressure (Pa @ 25 °C, EPI Suite)	50.93	19.07	18.27
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.74	4.23	2.86
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	$3.86E+01$	$1.26E+01$	$1.54E+02$
J_{\max} ($\mu\text{g}/\text{cm}^2/\text{h}$, SAM)	61.193	29.906	0.663
Henry's Law ($\text{Pa}\cdot\text{m}^3/\text{mol}$, Bond Method, EPI Suite)	$1.29E+02$	$1.71E+02$	$1.07E+01$
Repeated Dose Toxicity			
Repeated Dose (HESS)	<ul style="list-style-type: none"> • Not categorized 		<ul style="list-style-type: none"> • Not categorized

Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	● Non-binder, non-cyclic structure		● Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	● Non-toxicant (low reliability)		● Non-toxicant (low reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	● No alert found	● No alert found	
Protein Binding (OECD)	● No alert found	● No alert found	
Protein Binding Potency	● Not possible to classify according to these rules (GSH)	● Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	● No alert found	● No alert found	
Skin Sensitization Reactivity Domains (Toxtree v3.1.0)	● No skin sensitization reactivity domain alerts identified	● No skin sensitization reactivity domain alerts identified	
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

Summary

There are insufficient toxicity data on hexyl isobutyrate (CAS # 2349-07-7). 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, hexyl 2-methylbutyrate (CAS # 10032-15-2) and propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Hexyl 2-methylbutyrate (CAS # 10032-15-2) was used as a read-across analog for the target material hexyl isobutyrate (CAS # 2349-07-7) for the skin sensitization endpoint.
 - The target material and the read-across analog are structurally similar and belong to a class of saturated branched alkyl esters.
 - The target material and the read-across analog have a hexanol moiety and a similar branched acid moiety.
 - The key difference between the target material and the read-across analog is that the target material has an isobutyric acid group, whereas the read-across analog has a 2-methylbutyric acid 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.
 - There are no toxicological alerts for the target material as well as for the read-across analog. 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.
- Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) was used as a read-across analog for the target material hexyl isobutyrate (CAS # 2349-07-7) for the repeated dose toxicity and reproductive toxicity endpoints.
 - The target material and the read-across analog are structurally similar and belong to a class of saturated esters.
 - The target material and the read-across analog share a straight saturated alcohol moiety and a branched acid moiety.
 - The key difference between the target material and the read-across analog is that the target material has a hexanol group and an isobutyric acid group, whereas the read-across analog has a propanol group and a (2S)-2-(1,1-dimethylpropoxy)-propanoic acid group. These structural differences are 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 substance, 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.
 - There are no toxicological alerts for the target material as well as for the read-across analog. 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.

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