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Short Review

RIFM fragrance ingredient safety assessment, hexyl isovalerate, CAS Registry Number 10032-13-0

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phototoxicity/photoallergenicity
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ABSTRACT

Summary: The existing information supports the use of this material as described in this safety assessment. Hexyl isovalerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl isobutyrate (CAS # 2349-07-7) show that hexyl isovalerate is not expected to be genotoxic. Data on read-across analog 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 isovalerate is a skin sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; hexyl isovalerate 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 isovalerate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; hexyl isovalerate 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.

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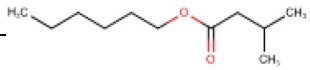


Name: Hexyl isovalerate
CAS Registry Number: 10032-13-0

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
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

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 isovalerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl isobutyrate (CAS # 2349-07-7) show that hexyl isovalerate is not expected to be genotoxic. Data on read-across analog 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 isovalerate is a skin sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; hexyl isovalerate 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 isovalerate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; hexyl isovalerate 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 expected to be 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 from do not indicate hexyl isovalerate 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:

Screening-level: 3.2 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Screening-level: 286.4 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 2.88 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: 2.88 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00288 μg/L

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

1. Identification

1. **Chemical Name:** Hexyl isovalerate
2. **CAS Registry Number:** 10032-13-0
3. **Synonyms:** Butanoic acid, 3-methyl-, hexyl ester; Hexyl isopentanoate; Hexyl isovalerianate; Hexyl 3-methylbutanoate; Hexyl-n isopentanoate; Hexyl isovalerate
4. **Molecular Formula:** $C_{11}H_{22}O_2$
5. **Molecular Weight:** 186.29
6. **RIFM Number:** 1145
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 213 °C (FMA), 218.34 °C (EPI Suite)
2. **Flash Point:** 190 °F; CC (FMA)
3. **Log K_{OW}:** 4.23 (EPI Suite)
4. **Melting Point**: 9.14 °C (EPI Suite)
5. **Water Solubility:** 12.56 mg/L (EPI Suite)
6. **Specific Gravity:** 0.852 (FMA), 0.8567 (RIFM)
7. **Vapor Pressure:** 0.0943 mm Hg @ 20 °C (EPI Suite v4.0), 0.06 mm Hg 20 °C (FMA), 0.143 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Arctander Volume I 1969: Colorless liquid. Somewhat pungent-fruity, “unripe"-fruity, slightly herbaceous, but rich and natural odor with a dry tobacco-leaf-like undertone. Sweet-green, heavy fruity, slightly herbaceous taste in dilutions lower than 20 ppm.

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95th Percentile Concentration in Hydroalcoholics:** 0.12% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000041 mg/kg/day or 0.0031 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0022 mg/kg/day (RIFM, 2017)

*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 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 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 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Hexyl isobutyrate (CAS # 2349-07-7)
   b. **Repeated Dose Toxicity:** Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1)
   c. **Reproductive Toxicity:** Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1)
   d. **Skin Sensitization:** Hexyl 2-methylbutyrate (CAS # 10032-15-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References

None.

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

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

Acerola (Malpighia).
Banana (*Musa sapientum* L.)
Capsicum species.
Cherimoya (*Annona cherimolia* Mill.)
Cider (apple wine).
Date (*Phoenix dactylifera* L.)
Lamb's lettuce (*Valerianella locusta*).

Mentha oils.
Nectarine.
Passion fruit (Passiflora species).
Wine.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 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 the current existing data and use levels, hexyl isovalerate does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Hexyl isovalerate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity (RIFM, 2013). 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 data assessing the mutagenic and clastogenic activity of hexyl isovalerate; however, read-across can be made to hexyl isobutyrate (CAS # 2349-07-7; see Section VI).

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 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, and this can be extended to hexyl isovalerate.

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 ethanol 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, and this can be extended to hexyl isovalerate.

Based on the available data, read-across material hexyl isobutyrate does not present a concern for genotoxic potential, and this can be extended to hexyl isovalerate.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for hexyl 2-methylbutyrate 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 isovalerate. Read-across material propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1; see Section VI) 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 low- and mid-dose groups. In the high-dose group, transient salivation was observed during the study starting on day 3. In addition, significant decreases were reported in erythrocyte count and mean corpuscular hemoglobin concentration. 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 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 isovalerate 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, 50/0.0022 or 22727.

In addition, the total systemic exposure to hexyl isovalerate (2.2 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 isovalerate 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 isovalerate. Read-across material propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1; see Section VI) 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 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 significant increased liver and kidney weights (high-dose F0 and F1 only), enlarged livers (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 incidental and attributed to xenobiotic administration as similar effects were also observed in the control group, 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 isovalerate 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 isovalerate, 250/0.0022 or 113636.

The hexyl isovalerate 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 isovalerate, 1000/0.0022 or 454545.

In addition, the total systemic exposure to hexyl isovalerate (2.2 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: 06/12/19.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Insufficient skin sensitization data is available on hexyl isovalerate. Existing data on read-across material hexyl 2-methylbutyrate (CAS # 10032-15-2; See Section VI) do not indicate that hexyl isovalerate 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 an *in vitro* KeratinoSens (RIFM, 2015). 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 6% or 4651 μg/cm^2 (RIFM, 1971). Additionally, in HRIPTs with 7086 μg/cm^2 (in 3:1 diethyl phthalate:ethanol) or 967 μg/cm^2 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, *in vitro*, and animal and human studies on read-across material hexyl 2-methylbutyrate, data do not indicate hexyl isovalerate 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 isovalerate 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 isovalerate 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 isovalerate 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} · 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 isovalerate 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 isovalerate. Based on the Creme RIFM Model, the inhalation exposure is 0.0031 mg/day. This exposure is 452 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 isovalerate 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 isovalerate 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 EPA, 2012a) did not identify hexyl isovalerate 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 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), hexyl isovalerate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Hexyl isovalerate has been pre-registered for REACH with no additional data at this time.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	4.23	4.23
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.00288 μg/L. The revised PEC/PNECs for EU and NA 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: 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/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 ap-

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.88			1000000	0.00288	

propriate 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.2020.111341.

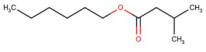
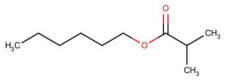
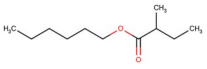
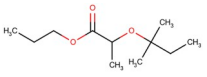
Appendix

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	Read-across Material
Principal Name	Hexyl isovalerate	Hexyl isobutyrate	Hexyl 2-methylbutyrate	Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate
CAS No.	10032-13-0	2349-07-7	10032-15-2	319002-92-1
Structure				
Similarity (Tanimoto Score)		0.80	0.86	0.42
Read-across Endpoint		• Genotoxicity	• Skin Sensitization	• Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_{11}H_{22}O_2$	$C_{10}H_{20}O_2$	$C_{11}H_{22}O_2$	$C_{11}H_{22}O_3$
Molecular Weight	186.295	172.268	186.295	202.294
Melting Point (°C, EPI Suite)	−9.14	−20.47	−9.14	3.41
Boiling Point (°C, EPI Suite)	218.34	198.83	218.34	219.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	19.07	50.93	19.07	18.27
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.23	3.74	4.23	2.86
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.26E+01	3.86E+01	1.26E+01	1.54E+02
J_{max} (μg/cm^2/h, SAM)	1.68	4.49	1.68	3.58
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.71E+02	1.29E+02	1.71E+02	1.07E+01
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found		
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	• Not classified	• Not classified		
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 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 v2.6.13)	• 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	• See Supplemental Data 4

Summary

There are insufficient toxicity data on hexyl isovalerate (CAS # 10032-13-0). 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, hexyl isobutyrate (CAS # 2349-07-7), 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 isobutyrate (CAS # 2349-07-7) was used as a read-across analog for the target material hexyl isovalerate (CAS # 10032-13-0) for the genotoxicity endpoint.
  - 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 hexanol and highly similar branched acid moieties.
  - The key difference between the target material and the read-across analog is that the target material has an isovaleric acid moiety, whereas the read-across analog has an isobutyric 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.
  - 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.
- Hexyl 2-methylbutyrate (CAS # 10032-15-2) was used as a read-across analog for the target material hexyl isovalerate (CAS # 10032-13-0) for the skin sensitization endpoint.
  - 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 hexanol and highly similar branched acid moieties.
  - The key difference between the target material and the read-across analog is that the target material has an isovaleric acid moiety, whereas the read-across analog has a 2-methylbutyric 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.
  - 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 isovalerate (CAS # 10032-13-0) 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 similar straight saturated alcohol moieties and similar branched acid moieties.
  - The key difference between the target material and the read-across analog is that the target material has a hexanol moiety and an isovaleric acid group, whereas the read-across analog has a propanol moiety 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.
  - 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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