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Short Review

RIFM fragrance ingredient safety assessment, hexyl 2-methylbutyrate, CAS Registry Number 10032-15-2



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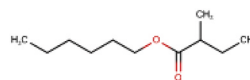
Genotoxicity
Repeated dose
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Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

Version: 050619. This version replaces any previous versions.

Name: Hexyl 2-methylbutyrate

CAS Registry Number: 10032-15-2

Abbreviation/Definition List:



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2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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 2-methylbutyrate 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 2-methylbutyrate 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. Existing data do not indicate that hexyl 2-methylbutyrate is a sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; hexyl 2-methylbutyrate 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 2-methylbutyrate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; hexyl 2-methylbutyrate 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: Derived 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: Existing data do not indicate hexyl 2-methylbutyrate is a sensitizer.

RIFM (2018a)

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: 67% (OECD 301F)

RIFM (2011)

Bioaccumulation:

Screening-level: 286 L/kg

(EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: 96-h Algae EC50: 0.609 mg/L

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1

Critical Ecotoxicity Endpoint: 96-h Algae EC50: 0.609 mg/L

RIFM PNEC is: 0.0609 µg/L

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

(ECOSAR; US EPA, 2012b)

(RIFM Framework; Salvito et al., 2002)

(ECOSAR; US EPA, 2012b)

1. Identification

- Chemical Name:** Hexyl 2-methylbutyrate
- CAS Registry Number:** 10032-15-2
- Synonyms:** Butanoic acid, 2-methyl-, hexyl ester; Hexyl 2-methylbutanoate; Cydrane; Hexyl 2-methylbutyrate
- Molecular Formula:** C₁₁H₂₂O₂
- Molecular Weight:** 186.29
- RIFM Number:** 977
- Stereochemistry:** One stereocenter present and 2 stereoisomers possible.

2. Physical data

- Boiling Point:** > 212 °C (FMA), 218.34 °C (EPI Suite)
- Flash Point:** 85 °C (GHS), 185 °F; CC (FMA)
- Log KOW:** Log Pow = 4.4 (RIFM, 2013a), 4.23 (EPI Suite)
- Melting Point:** 9.14 °C (EPI Suite)
- Water Solubility:** 12.56 mg/L (EPI Suite)
- Specific Gravity:** 0.856 (FMA)
- 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)
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol⁻¹ · cm⁻¹)
- Appearance/Organoleptic:** Arctander Volume I 1969: Colorless liquid. Powerful, fresh-green fruity odor. Overall somewhat sharp in its note. Sweet, fruity-green taste, reminiscent of unripe strawberries.

3. Volume of use (Worldwide band)

- 1–10 metric tons per year (IFRA, 2015)

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

- | | |
|---|--------------|
| 1. 95th Percentile Concentration in Hydroalcohols: 0.021% | RIFM (2018b) |
| 2. Inhalation Exposure*: 0.00012 mg/kg/day or 0.0094 mg/day | RIFM (2018b) |
| 3. Total Systemic Exposure**: 0.00094 mg/kg/day | RIFM (2018b) |

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford et al., 2015, 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, 2015, 2017; Safford et al., 2015, 2017).

5. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

6. Computational toxicology evaluation

- Cramer Classification: Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:

- Genotoxicity:** Hexyl isobutyrate (CAS # 2349-07-7)
 - 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:** None
 - Phototoxicity/Photoallergenicity:** None
 - Local Respiratory Toxicity:** None
 - Environmental Toxicity:** None
- 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 2-methylbutyrate is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species) Apple processed (*Malus* species) Apricot (*Prunus armeniaca* L.) Cherimoya (*Annona cherimolia* Mill.) Grape (*Vitis* species) Passion fruit (*Passiflora* species) Spineless monkey orange (*Strychnos madagasc.*) 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. This is a partial list.

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, hexyl 2-methylbutyrate does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Hexyl 2-methylbutyrate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity (RIFM, 2013b). 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 2-methylbutyrate; 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 2-methylbutyrate.

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 2-methylbutyrate.

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 2-methylbutyrate.

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 2-methylbutyrate. 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 the 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 counts and mean corpuscular hemoglobin concentration, and increases in mean corpuscular volume were reported as well. 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 2-methylbutyrate 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, 50/0.00094 or 53191.

In addition, the total systemic exposure to hexyl 2-methylbutyrate (0.94 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007) 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 2-methylbutyrate 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 2-methylbutyrate. 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 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 doses 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 of 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 2-methylbutyrate 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 2-methylbutyrate, 250/0.00094 or 265957.

The hexyl 2-methylbutyrate 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 2-methylbutyrate, 1000/0.00094 or 1063830.

In addition, the total systemic exposure to hexyl 2-methylbutyrate (0.94 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007; Laufersweiler, 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

The existing data do not indicate that hexyl 2-methylbutyrate is a sensitizer.

11.1.4.1. Risk assessment. Existing data do not indicate hexyl 2-methylbutyrate is a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree 3.1.0). Hexyl 2-methylbutyrate was found to be negative in an *in chemico* Direct Peptide Reactivity Assay (DPRA) and *in vitro* KeratinoSens (RIFM, 2015). Furthermore, in a guinea pig open epicutaneous test (OET), hexyl 2-methylbutyrate did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed in 33 subjects at 10% hexyl 2-methylbutyrate in petrolatum (RIFM, 1977). Additionally, in a confirmatory human repeat insult patch tests (HRIPT) with 7086 µg/cm² in 3:1 diethyl phthalate:EtOH or 967 µg/cm² of hexyl 2-methylbutyrate in alcohol SDA 39C, no reactions indicative of sensitization was observed in any of the 109 or 38 volunteers, respectively (RIFM, 2018a; RIFM, 1972).

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

Additional References: Natsch et al. (2007); McKim et al. (2010).

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hexyl 2-methylbutyrate 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 2-methylbutyrate 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 2-

methylbutyrate 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 for hexyl 2-methylbutyrate 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 2-methylbutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.0094 mg/day. This exposure is 148.9 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 2-methylbutyrate 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 2-methylbutyrate 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 2-methylbutyrate 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 BLOWIN 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 2-methylbutyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Biodegradation. RIFM, 2011: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 67% was observed after 28 days.

11.2.2.2. Ecotoxicity. No data available.

11.2.3. Other available data

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

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

Endpoints used to calculate PNEC are underlined.

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

The RIFM PNEC is 0.0609 µg/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

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>2.05</u>			1000000	0.00205	
ECOSAR Acute Endpoints (Tier 2) v1.11	1.244	2.038	<u>0.609</u>	10000	0.0609	Esters
ECOSAR Acute Endpoints (Tier 2) v1.11	1.526	1.064	1.85			Neutral Organic SAR

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

Exposure	Europe	North America
Log K_{ow} Used	4.4	4.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
Risk Characterization: PEC/PNEC	< 1	< 1

- **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.

13. Conflicts of interest

The authors declare that they have no conflicts of interest.

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.2020.111463>.

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 2-methylbutyrate	Hexyl isobutyrate	Propyl (2S)-2-(1,1-dimethylproxy)-propanoate
CAS No.	10032-15-2	2349-07-7	319002-92-1
Structure			
Similarity (Tanimoto Score)		0.94	0.41
Read-across Endpoint		<ul style="list-style-type: none"> • Genotoxicity 	<ul style="list-style-type: none"> • Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	C ₁₁ H ₂₂ O ₂	C ₁₀ H ₂₀ O ₂	C ₁₁ H ₂₂ O ₃
Molecular Weight	186.295	172.268	202.294
Melting Point (°C, EPI Suite)	-9.14	-20.47	3.41
Boiling Point (°C, EPI Suite)	218.34	198.83	219.10
Vapor Pressure (Pa @ 25 °C, EPI Suite)	19.07	50.93	18.27
Log K _{ow} (KOWWIN v1.68 in EPI Suite)	4.23	3.74	2.86
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.26E+01	3.86E+01	1.54E+02
J_{\max} (µg/cm ² /h, SAM)	29.906	61.193	0.663
Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	1.71E+02	1.29E+02	1.07E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found
Carcinogenicity (ISS)	<ul style="list-style-type: none"> • Structural alert for non-genotoxic carcinogenicity Substituted n-alkylcarboxylic acids (Non-genotoxic) 	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found
<i>In Vitro</i> Mutagenicity (Ames, ISS)	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • No alert found 	<ul style="list-style-type: none"> • 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)	● Toxicant (low reliability)	● Non-toxicant (low reliability)
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 2-methylbutyrate (CAS # 10032-15-2). 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) 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 2-methylbutyrate (CAS # 10032-15-2) 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.
 - The target material presents a carcinogenicity alert for substituted n-alkylcarboxylic acids, which is not found for the read-across analog. This alert is due to the methyl β -substitution within an aliphatic acid branch. Substances belonging to this chemical class are potentially reactive as peroxisome proliferators (PPs). PPs are a diverse group of chemicals, including hypolipidemic drugs, plasticizers, and herbicides, that were found to cause liver cancer when chronically administered to rats and mice. These chemicals are considered non-genotoxic agents, given generally negative results in genotoxicity assays. Even if the mechanism by which these chemicals cause tumors is not fully understood, peroxisome proliferator-activated receptor alpha (PPAR α) is thought to mediate most of the PP effects in the rodent liver. The data described in the genotoxicity section shows that the MOE is adequate at the current level of use. The predictions are therefore superseded by 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.
- Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) was used as a read-across analog for the target material hexyl 2-methylbutyrate (CAS # 10032-15-2) 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.
 - 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 for the repeated dose 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.

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