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RIFM fragrance ingredient safety assessment, octyl isobutyrate, CAS Registry Number 109-15-9

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ABSTRACT

The existing information supports **the use of this material as described in this safety assessment**. Octyl isobutyrate 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 octyl isobutyrate is not expected to be genotoxic. Data on analog propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from analog hexyl 2-methylbutyrate (CAS # 10032-15-2) provided octyl isobutyrate a No Expected Sensitization Induction Level (NESIL) of 7000 μg/cm^2 for the skin sensitization endpoint. Octyl isobutyrate is not expected to be phototoxic/photoallergenic based on ultraviolet/visible (UV/Vis) spectra. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure to is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; octyl isobutyrate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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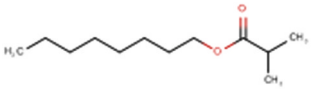

Name: Octyl isobutyrate
CAS Registry Number: 109-15-9

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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 Observed 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

(*continued on next column*)

(*continued*)

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.

Octyl isobutyrate 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 octyl isobutyrate is not expected to be genotoxic. Data on analog propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from analog hexyl 2-methylbutyrate (CAS # 10032-15-2) provided octyl isobutyrate a No Expected Sensitization Induction Level (NESIL) of 7000 μg/cm^2 for the skin sensitization endpoint. Octyl isobutyrate is not expected to be phototoxic/photoallergenic based on ultraviolet/visible (UV/Vis) spectra. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure to is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; octyl isobutyrate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2003; RIFM, 2014b)

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

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

Skin Sensitization: NESIL = 7000 μg/cm^2. RIFM (2018)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 3.1 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 167 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: 96-h Algae EC50: 0.297 mg/L (ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

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

Critical Ecotoxicity Endpoint: 96-h Algae EC50: 0.297 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.02097 μg/L

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

1. Identification

1. **Chemical Name:** Octyl isobutyrate
2. **CAS Registry Number:** 109-15-9
3. **Synonyms:** Octyl 2-methylpropanoate; Propanoic acid, 2-methyl-, octyl ester; 脂肪酸(C = 4~10)アルキル(又はアルケニル) (C = 8~24); Octyl isobutyrate
4. **Molecular Formula:** $C_{12}H_{24}O_2$
5. **Molecular Weight:** 200.32
6. **RIFM Number:** 604
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 236.95 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 4.72 (EPI Suite)
4. **Melting Point**: 1.93 °C (EPI Suite)
5. **Water Solubility:** 4.064 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.035 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0544 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficients (0, 0, and 126 L mol^{-1} • cm^{-1}, under neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid

3. Volume of use (Worldwide Band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.2)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.015% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.000064 mg/kg/day or 0.0049 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00091 mg/kg/day (RIFM, 2020b)

*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; 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; 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 v3.1	OECD QSAR Toolbox v4.2
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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

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

Babaco fruits (*Carica pentagona* Heilborn).
Citrus fruits.
Hop (*Humulus lupulus*).
Mangifera species.

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

9. REACH dossier

Octyl isobutyrate has been pre-registered for 2010; no dossier available as of 12/08/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for octyl isobutyrate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.20
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	0.40
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.00015
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.16
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.000050
6	Products with oral and lip exposure	1.1
7	Products applied to the hair with some hand contact	0.20
8	Products with significant ano-genital exposure (tampon)	0.000050
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.6
10B	Aerosol air freshener	3.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.000050
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	40

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For octyl isobutyrate, the basis was the subchronic reference dose of 0.50 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, octyl isobutyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Octyl isobutyrate was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: <80% relative cell density), negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2014a). BlueScreen 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 octyl isobutyrate; 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 octyl isobutyrate.

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 dose range finding (DRF) study. Micronuclei analysis was conducted at concentrations up to 400 μg/mL in the presence and absence of 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, 2014b). 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 octyl isobutyrate.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

The MOE for octyl isobutyrate 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 octyl isobutyrate. Read-across analog 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 counts 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. Based on the treatment-related alterations of hematology and 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; ECHA, 2012b).

A default safety factor of 3 was applied as the above NOAEL from the 28-day OECD 407 study (ECHA, 2012a). 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 octyl 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, 50/0.00091, or 54945.

In addition, the total systemic exposure to octyl isobutyrate (0.91 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.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020c) and a subchronic reference dose (RfD) of 0.50 mg/kg/day.

Derivation of subchronic RfD:

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for octyl isobutyrate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.50 mg/kg/day.

*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: 03/03/21.

11.1.3. Reproductive toxicity

The MOE for octyl 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 octyl isobutyrate. 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 the 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 the 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 livers (high-dose F1 only), and microscopic alterations in the livers (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 octyl 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 octyl isobutyrate, 250/0.00091 or 274725.

The octyl 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 octyl isobutyrate, 1000/0.00091 or 1098901.

In addition, the total systemic exposure to octyl isobutyrate (0.91 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: 03/05/21.

11.1.4. Skin sensitization

Based on the existing data and read-across hexyl 2-methylbutyrate (CAS # 10032-15-2), octyl isobutyrate is considered a skin sensitizer with a defined NESIL of 7000 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization data are available for octyl isobutyrate. Based on the existing data and read-across material hexyl 2-methylbutyrate (CAS # 10032-15-2; see Section VI), octyl isobutyrate is considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, hexyl 2-methylbutyrate, was found to be negative in the *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay (RIFM, 2015b; RIFM, 2015a). In a murine local lymph node assay (LLNA), read-across material hexyl 2-methylbutyrate was found to be sensitizing with an EC3 value of 54.8% (13700 μg/cm^2) (RIFM, 2000). However, the results from this LLNA may be suboptimal since the test was conducted in the unvalidated range (>25%) of the OECD guideline (Kolle et al., 2020). 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 octyl isobutyrate and read-across material hexyl 2-methylbutyrate at 2% (1380 μg/cm^2) and 10% (6900 μg/cm^2) in petrolatum, respectively (RIFM, 1977b; RIFM, 1977a). In Confirmation of No Induction in Humans tests (CNIHs) with read-across material hexyl 2-methylbutyrate at 7086 μg/cm^2 in 3:1 diethyl phthalate:EtOH or 967 μg/cm^2 in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 109 or 38 volunteers, respectively (RIFM, 2018; RIFM, 1972).

Based on the weight of evidence (WoE) from structural analysis and human studies on the read-across material hexyl 2-methylbutyrate and the target material, octyl isobutyrate is a weak sensitizer with a WoE NESIL of 7000 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020c) and a subchronic reference dose of 0.50 mg/kg/day.

Additional References: Natsch et al., 2007; McKim et al., 2010.

Literature Search and Risk Assessment Completed On: 02/23/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, octyl 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 octyl isobutyrate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, octyl isobutyrate does not present a concern for phototoxicity or photoallergenicity.

Table 1
Data summary for hexyl 2-methylbutyrate as read-across material for octyl isobutyrate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
13700 [1]	Weak	7086	6900	NA	7000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (0, 0, and 126 L mol^{-1} • cm^{-1}, under neutral, acidic, and basic conditions, respectively) are 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: 03/02/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level of octyl 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 octyl isobutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.0049 mg/day. This exposure is 285.7 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: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of octyl 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, octyl 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 octyl isobutyrate as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), octyl isobutyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Octyl isobutyrate has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation.

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	4.72	4.72
Biodegradation Factor Used	1	1
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 0.02097 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 VoU.

Literature Search and Risk Assessment Completed On: 03/09/21.

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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.16			1000000	0.00116	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.691	1.074	0.297	10000	0.0297	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.594	0.434	0.912			Neutral Organic SAR

links listed above were active as of 12/08/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112870.

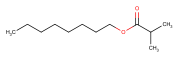
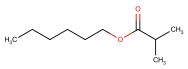
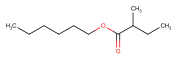
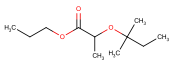
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (Schultz et al., 2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Octyl isobutyrate	Hexyl isobutyrate	Hexyl 2-methylbutyrate	Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate
CAS No.	109-15-9	2349-07-7	10032-15-2	319002-92-1
Structure				
Similarity (Tanimoto Score)		0.94	0.88	0.41
Read-across Endpoint		• Genotoxicity	• Skin Sensitization	• Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_{12}H_{24}O_2$	$C_{10}H_{20}O_2$	$C_{11}H_{22}O_2$	$C_{11}H_{22}O_3$
Molecular Weight	200.32	172.26	186.29	202.29
Melting Point (°C, EPI Suite)	1.93	−20.47	−9.14	3.41
Boiling Point (°C, EPI Suite)	236.95	198.83	218.34	219.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.25	50.93	19.07	18.27
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.72	3.74	4.23	2.86
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.06E+00	3.86E+01	1.26E+01	1.54E+02
J_{max} (μg/cm^2/h, SAM)	11.77	4.49	1.68	3.58
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.28E+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 octyl isobutyrate (CAS # 109-15-9). 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 octyl isobutyrate (CAS # 109-15-9) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated esters.
  - o The target material and the read-across analog share highly similar straight saturated alcohols and isobutyric acid moieties.
  - o The key difference between the target material and the read-across analog is that the target material has an octanol moiety, whereas the read-across analog has a hexanol moiety. This structural difference is toxicologically insignificant.
  - o The 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.
  - o 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 ≤80% and J_{max} for the read-across analog corresponds to skin absorption ≤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.

- Hexyl 2-methylbutyrate (CAS # 10032-15-2) was used as a read-across analog for the target material octyl isobutyrate (CAS # 109-15-9) 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 highly similar straight saturated alcohol and branched acid moieties.
  - The key difference between the target material and the read-across analog is that the target material has octanol and isobutyric acid groups, whereas the read-across analog has hexanol and 2-methylbutyric acid groups. These structural differences are toxicologically insignificant.
  - The 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 ≤80% and J_{max} for the read-across analog corresponds to skin absorption ≤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.
- Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate (CAS # 319002-92-1) was used as a read-across analog for the target material octyl isobutyrate (CAS # 109-15-9) 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 highly similar straight saturated alcohol and similar branched acid moieties.
  - The key difference between the target material and the read-across analog is that the target material has octanol and isobutyric acid groups, whereas the read-across analog has propanol and (2S)-2-(1,1-dimethylpropoxy)-propanoic acid groups. These structural differences are toxicologically insignificant.
  - The 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 ≤80% and J_{max} for the read-across analog corresponds to skin absorption ≤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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