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RIFM fragrance ingredient safety assessment, ethyl isovalerate, CAS Registry Number 108-64-5

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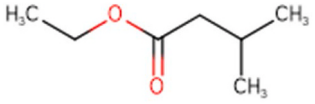

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Name: Ethyl isovalerate
CAS Registry Number: 108-64-5

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

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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., 2020)
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., 2017; Safford et al., 2015a; Safford et al., 2017; Comiskey 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 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.

Ethyl isovalerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog methyl isovalerate (CAS # 556-24-1) show that ethyl isovalerate is not expected to be genotoxic. Data from read-across analog ethyl-2-methylbutyrate (CAS # 7452-79-1) provided an MOE >100 for the repeated dose and reproductive toxicity endpoints. Target data and read-across data from ethyl isobutyrate (CAS # 97-62-1) and methyl 2-methylbutyrate (CAS # 868-57-5) show that there are no safety concerns for ethyl isovalerate for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; ethyl 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 ethyl isovalerate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; ethyl isovalerate was found not to be a 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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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 2015e; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methylbutyrate; ECHA, 2013)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methylbutyrate; ECHA, 2013)
Skin Sensitization: No safety concern for skin sensitization at the current, declared use levels.	(RIFM, 1985; ECHA REACH Dossier: Ethyl Isobutyrate; ECHA, 2017a)
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:	
Critical Measured Value: Critical Measured Value: 65% (OECD 301D)	RIFM (1999)
Bioaccumulation:	
Screening-level: Screening-level: 14.48 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Screening-level: Fish LC50: 68.49 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: 68.49 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.06849 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Ethyl isovalerate
2. **CAS Registry Number:** 108-64-5
3. **Synonyms:** Butanoic acid, 3-methyl-, ethyl ester; Ethyl isopentanoate; Ethyl isovalerianate; Ethyl 3-methylbutanoate; Ethyl β-methylbutyrate; Ethyl isovalerianat; ペンタン酸アルキル（C = 1 ~ 5）; Ethyl isovalerate
4. **Molecular Formula:** $C_7H_{14}O_2$
5. **Molecular Weight:** 130.18
6. **RIFM Number:** 750
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 135 °C (Fragrance Materials Association [FMA]), 134.87 °C (EPI Suite), 135.3 °C at 1013 hPa (RIFM, 2015c)
2. **Flash Point:** 35 °C (Globally Harmonized System [GHS]), 95 °F; CC (FMA), 28.0 °C (average corrected and rounded down to the nearest 0.5 °C) (RIFM, 2015d)
3. **Log K_{OW}:** 2.26 (EPI Suite), 2.47 at 23.8 °C (RIFM, 2015b)
4. **Melting Point**: 56.05 °C (EPI Suite), no melting point down to −100 °C at 1011–1013 hPa (RIFM, 2015c)

5. **Water Solubility:** 1070 mg/L (EPI Suite)
6. **Specific Gravity:** 0.862–0.866 (FMA), 0.864–0.868 (FMA)
7. **Vapor Pressure:** 5.86 mm Hg at 20 °C (EPI Suite v4.0), 5.9 mm Hg at 20 °C (FMA), 7.98 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless to very pale yellow, oily liquid, with a strong fruity odor reminiscent of apple

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.077% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.00040 mg/kg/day or 0.030 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0023 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 2015a; 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 (RIFM, 2015a; 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 v3.1	OECD QSAR Toolbox v4.2
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2. Analogs Selected:
   a. **Genotoxicity:** Methyl isovalerate (CAS # 556-24-1)
   b. **Repeated Dose Toxicity:** Ethyl-2-methylbutyrate (CAS # 7452-79-1)
   c. **Reproductive Toxicity:** Ethyl-2-methylbutyrate (CAS # 7452-79-1)
   d. **Skin Sensitization:** Read-across: ethyl isobutyrate (CAS # 97-62-1); methyl 2-methylbutyrate (CAS # 868-57-5); Weight of evidence (WoE): isoamyl acetate (CAS # 123-92-2)
   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

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

Acerola (*Malpighia*)
Apple brandy (*Calvados*)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Artocarpus species
Banana (*Musa sapientum* L.)
Beer
Bilberry wine
Camomile
Cape gooseberry (*Physalis peruviana* L.)
Capsicum species
Cashew apple (*Anacardium occidentale*)
Cashew apple wine
Celery (*Apium graveolens* L.)
Cheese, various types
Cherimoya (*Annona cherimolia* Mill.)
Chinese quince (*Pseudocydonia sinensis* Schneid)
Cider (apple wine)
Citrus fruits
Cocoa category
Date (*Phoenix dactylifera* L.)
Durian (*Durio zibethinus*)Dwarf quince (*Chaenomeles japonica*)
Fish
Gabiroba (*Campomanesia xanthocarpa*)
Grape brandy
Guava wine
Honey
Hop (*Humulus lupulus*)
Kiwifruit (*Actinidia chinensis, syn. A. Deliciosa*)
Mangifera species
Marula (*Sclerocarya birrea* subsp. Caffra)
Melon
Milk and milk products
Mountain papaya (*c. Candamarcensis, c. Pubescens*)
Mussel
Naranjilla fruit (*Solanum quitoense* Lam.)
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species)
Passion fruit wine
Pear (*Pyrus communis* L.)
Pear brandy
Peas (*Pisum sativum* L.)
Pineapple (*Ananas comosus*)
Plum (*Prunus* species)
Pomegranate juice (*Punica granatum* L.)
Pork
Quince, marmelo (*Cydonia oblonga* Mill.)
Raspberry, blackberry, and boysenberry
Rum
Sake
Salami
Sherry
Soybean (*Glycine max.* L. Merr.)
Strawberry (*Fragaria* species)
Strawberry wine
Sugar molasses
Swiss cheeses
Tequila (*Agave tequilana*)

Vaccinium species
Vinegar
Whisky
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

Available; accessed 10/11/21 (ECHA, 2018)

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, ethyl isovalerate does not present a concern for genotoxicity.

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

The mutagenic activity of ethyl isovalerate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 (OECD, 2015) using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with ethyl isovalerate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015e). Under the conditions of the study, ethyl isovalerate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of ethyl isovalerate; however, read-across can be made to methyl isovalerate (CAS # 556-24-1; see Section VI). The clastogenic activity of methyl isovalerate 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 methyl isovalerate in DMSO at concentrations up to 1160 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Methyl isovalerate did not induce binucleated cells with micronuclei when tested up to cytotoxic concentration levels in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, methyl isovalerate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl isovalerate does not present a concern for genotoxic potential.

Additional References: ECHA, 2018.

Literature Search and Risk Assessment Completed On: 03/11/21.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for ethyl isovalerate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on ethyl isovalerate. Read-across material, ethyl 2-methylbutrate (CAS # 7452-79-1; see Section VI) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days, and females were treated for 40–51 days (maximum of 51 days, males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. No treatment-related adverse effects were reported for mortality, clinical signs, neurobehavior, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, pathological findings during necropsy, or histopathological examination. The NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 1000/3, or 333 mg/kg/day.

Therefore, the ethyl isovalerate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to ethyl isovalerate, 333/0.0023, or 144783.

In addition, the total systemic exposure to ethyl isovalerate (2.3 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: 02/23/21.

11.1.3. Reproductive toxicity

The MOE for ethyl isovalerate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on ethyl isovalerate. Read-across material, ethyl 2-methylbutrate (CAS # 7452-79-1; see Section VI) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days, and females were treated for 40–51 days (maximum of 51 days, males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. There were no treatment-related effects on mating performance, fertility, conception, gestation length, parturition, survival, litter size, or litter weight. In the F1 generation, no treatment-related effects were reported for mortality, clinical signs, body weight, and bodyweight changes during necropsy. Furthermore, no gross abnormalities were reported in pups. Therefore, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

Therefore, the ethyl isovalerate MOE for the reproductive toxicity endpoint can be calculated by dividing ethyl 2-methylbutrate NOAEL in mg/kg/day by the total systemic exposure to ethyl isovalerate, 1000/0.0023, or 434783.

In addition, the total systemic exposure to ethyl isovalerate (2.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/01/21.

11.1.4. Skin sensitization

Based on existing data and data on read-across materials ethyl isobutyrate (CAS # 97-62-1) and methyl 2-methylbutyrate (CAS # 868-57-5) and WoE material isoamyl acetate (CAS # 123-92-2), ethyl isovalerate does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for ethyl isovalerate. Based on existing data and read-across to ethyl isobutyrate (CAS # 97-62-1; see Section VI) and methyl 2-methylbutyrate (CAS # 868-57-5; see Section VI) and WoE material isoamyl acetate (CAS # 123-92-2; see Section VI), ethyl isovalerate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.0.1; OECD Toolbox v4.2). In guinea pigs, maximization tests with read-across analogs ethyl isobutyrate and methyl 2-methylbutyrate and WoE isoamyl acetate did not present reactions indicative of sensitization (RIFM, 1985; ECHA, 2017a; Ballantyne et al., 1986). In human maximization tests, no skin sensitization reactions were observed with ethyl isovalerate or read-across materials ethyl isobutyrate and methyl 2-methylbutyrate and WoE material isoamyl acetate (RIFM, 1976; RIFM, 1982; RIFM, 1975; RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 20% or 23622 μg/cm^2 of WoE material isoamyl acetate in 75:25 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 197 volunteers (RIFM, 1987).

Based on WoE from structural analysis, animal and human studies, and data from analogs ethyl isobutyrate and methyl 2-methylbutyrate and isoamyl acetate (WoE material), ethyl isovalerate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: Klecak (1985).

Literature Search and Risk Assessment Completed On: 02/28/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl 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 ethyl isovalerate in experimental models. UV/Vis absorption spectra indicate no absorption 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, ethyl 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 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: 02/18/21.

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on ethyl isovalerate. Based on the Creme RIFM Model, the inhalation exposure is 0.030 mg/day. This exposure is 46.7 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: RIFM, 1980; UGCM, 1997

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 ethyl 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, ethyl 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 ethyl 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, 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1999:** A study was performed to assess the biodegradability of the test material using the closed bottle test according to the OECD 301D method. Biodegradation of 65% was observed after 26 days.

11.2.2.1.2. Ecotoxicity. **RIFM, 1999:** A *Daphnia magna* immobilization test was conducted according to 92/69/EEC C.2 method under static conditions. The 48-h EC0 value obtained for the test material was ≥ 73 mg/L (nominal) and ≥ 67 mg/L (measured).

RIFM, 2016: A fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h EC50 value based on the geometric mean of LC100/LC0 based on mean measured concentration was reported to be 8.45 mg/L.

RIFM, 2017b: The algae growth inhibition test was conducted according to the OECD 201 guideline, under static conditions. The 72-h EC50 values based on nominal concentration for growth rate and yield were reported to be 124 mg/L and 75.3 mg/L, respectively. The 72-h EC10 values based on nominal concentration for growth rate and yield were reported to be 73.6 mg/L and 43.5 mg/L, respectively.

11.2.2.1.3. Other available data. Ethyl isovalerate has been registered under REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since ethyl isovalerate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	68.49			1000000	0.06849	

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

Exposure	Europe	North America
Log K_{ow} Used	2.47	2.47
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.06845 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 VoU.

Literature Search and Risk Assessment Completed On: 03/08/21.

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 links listed above were active as of 10/11/21.

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.2021.112724.

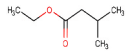
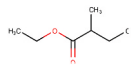
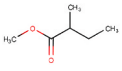
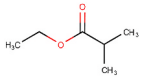
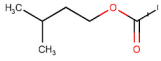
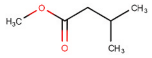
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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 Chemical Agency read-across assessment framework (ECHA, 2017b).

- 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), and skin sensitization was predicted using Toxtree 2.6.13.
- 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).

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material	Read-across Material
Principal Name	Ethyl isovalerate	Ethyl 2-methylbutyrate	Methyl 2-methylbutyrate	Ethyl isobutyrate	Isoamyl acetate	Methyl isovalerate
CAS No.	108-64-5	7452-79-1	868-57-5	97-62-1	123-92-2	556-24-1
Structure						
Similarity (Tanimoto Score)		0.85	0.68	0.64	0.76	0.96
Read-across Endpoint		• Repeated dose Toxicity • Reproductive Toxicity	• Skin sensitization	• Skin sensitization	• Skin sensitization	• Genotoxicity
Molecular Formula	$C_7H_{14}O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$	$C_6H_{12}O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$
Molecular Weight	130.19	130.19	116.16	116.16	130.187	116.16
Melting Point (°C, EPI Suite)	−56.05	−56.05	−68.43	−68.43	−78.50	−68.43
Boiling Point (°C, EPI Suite)	134.87	134.87	111.74	111.74	142.50	111.74
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.06E+003	1.07E+003	3E+003	3E+003	7.47E+02	2.44E+003
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	2.26	2.26	1.77	1.77	2.00E+03	1.82
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2000	1070	3172	3172	2.25	2892
J_{max} (μg/cm^2/h, SAM)	63.090	297.516	440.615	460.179	101.63	465.295
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.52E+001	5.52E+001	4.16E+001	4.16E+001	5.95E+01	4.16E+001
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)	• Non-carcinogen (low reliability)					• Non-carcinogen (low reliability)
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

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material	Read-across Material
Repeated Dose Toxicity						
Repeated Dose (HESS)	• Not categorized	• Not categorized				
Reproductive Toxicity						
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, cyclic structure	• Non-binder, 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	• No alert found	• No alert found	
Protein Binding (OECD)	• No alert found		• No alert found	• No alert found	• No alert found	
Protein Binding Potency	• Not possible to classify		• Not possible to classify	• Not possible to classify	• Not possible to classify	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found	• No alert found	• No alert found	
Metabolism						
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5	See Supplemental Data 6

Summary

There are insufficient toxicity data on ethyl isovalerate (CAS # 108-64-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, ethyl 2-methylbutyrate (CAS # 7452-79-1), methyl 2-methylbutyrate (CAS # 868-57-5), ethyl isobutyrate (CAS # 97-62-1), isoamyl acetate (CAS # 123-92-2) (WoE), and methyl isovalerate (CAS # 556-24-1) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 2-methylbutyrate (CAS # 7452-79-1) was used as a read-across analog for the target material ethyl isovalerate (CAS # 108-64-5) for the repeated dose and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - o The target material and the read-across analog are ethyl esters of similar branched-chain acids.
  - o The key structural difference between the target material and the read-across analog is that the target material is the ethyl ester of isovaleric acid, whereas the read-across analog is the ethyl ester of 2-methylbutyric acid. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these branched ethyl ester structures. 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 comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Methyl 2-methylbutyrate (CAS # 868-57-5) was used as a read-across analog for the target material ethyl isovalerate (CAS # 108-64-5) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - o The target material and the read-across analog share similar branched ester structures.
  - o The key structural difference between the target material and the read-across analog is that the target material is the ethyl ester of isovaleric acid, whereas the read-across analog is the methyl ester of 2-methylbutyric acid. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these branched ethyl ester structures. 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 comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.
- Ethyl isobutyrate (CAS # 97-62-1) was used as a read-across analog for the target material ethyl isovalerate (CAS # 108-64-5) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - o The target material and the read-across analog are ethyl esters of similar branched-chain acids.

- The key structural difference between the target material and the read-across analog is that the target material is the ethyl ester of isovaleric acid, whereas the read-across analog is the ethyl ester of isobutyric acid. This structural difference is toxicologically insignificant.
- Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these branched ethyl ester structures. 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 comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

- Isoamyl acetate (CAS # 123-92-2) was used as a WoE material for the target material ethyl isovalerate (CAS # 108-64-5) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - The target material and the read-across analog are ethyl esters of similar branched-chain acids.
  - The key structural difference between the target material and the read-across analog is that the target material is the ethyl ester of isovaleric acid, whereas the read-across analog is the ethyl ester of isobutyric acid. This structural difference is toxicologically insignificant.
  - Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these branched ethyl ester structures. 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 comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.
- Methyl isovalerate (CAS # 556-24-1) was used as a read-across analog for the target material ethyl isovalerate (CAS # 108-64-5) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - The target material and the read-across analog are both isovalerate esters.
  - The key structural difference between the target material and the read-across analog is that the target material is the ethyl ester of isovaleric acid, whereas the read-across analog is the methyl ester of isovaleric acid. This structural difference is toxicologically insignificant.
  - Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these isovalerate ester structures. 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 comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for the toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator. The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

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