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Short Review

RIFM fragrance ingredient safety assessment, ethyl 2-ethylhexanoate, CAS Registry Number 2983-37-1

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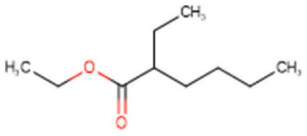

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Name: Ethyl 2-ethylhexanoate CAS Registry Number: 2983-37-1

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations

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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., 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; B. Safford et al., 2015; B. Safford et al., 2024; B. 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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.

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Summary: The existing information supports the use of this material as described in this safety assessment.

Ethyl 2-ethylhexanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog ethyl 2-methylpentanoate (CAS # 39255-32-8) show that ethyl 2-ethylhexanoate is not expected to be genotoxic. Data on read-across analog ethyl 2-methylbutyrate (CAS # 7452-79-1) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog butyl 2-methylvalerate (CAS # 6297-41-2) show that there are no safety concerns for ethyl 2-ethylhexanoate for skin sensitization under the current declared levels of use. The photoirritation endpoint was evaluated based on data and ultraviolet/visible (UV/Vis) spectra; ethyl 2-ethylhexanoate is not photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis spectra; ethyl 2-ethylhexanoate is not expected to be photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to ethyl 2-ethylhexanoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; ethyl 2-ethylhexanoate 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 (VoU) 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.	(ECHA, 2017a; ECHA, 2013b)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA, 2013a)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA, 2013a)
Skin Sensitization: No concern for skin sensitization.	(RIFM, 2023b; RIFM, 2023a)
Photoirritation/Photoallergenicity: Not photoirritating/not expected to be photoallergenic.	UV/Vis Spectra, RIFM Database; RIFM, 1976)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Screening-level: 3.25 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 135 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 7. 70 mg/L	(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	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 7.70 mg/L	(Salvito et al., 2002)

RIFM PNEC is: 0.00770 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable, cleared at the screening-level

1. Identification

1. **Chemical Name:** Ethyl 2-ethylhexanoate
2. **CAS Registry Number:** 2983-37-1
3. **Synonyms:** Hexanoic acid, 2-ethyl-, ethyl ester; Irotyl; Ethyl α-ethylcaproate; Ethyl 2-ethylcaproate; ｱﾙｶﾝ酸(C = 6 ~ 10)ｱﾙｷﾙ(C = 1 ~ 10); Ethyl 2-ethylhexanoate
4. **Molecular Formula:** $C_{10}H_{20}O_2$
5. **Molecular Weight:** 172.26 g/mol
6. **RIFM Number:** 1208
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** Kp18 81 °C (Henkel), 198.83 °C (EPI Suite v4.11)
2. **Flash Point:** 67 °C (Globally Harmonized System), 67 °C (Henkel)

3. **Log K_{OW}:** 3.74 (EPI Suite v4.11)
4. **Melting Point**: −20.47 °C (EPI Suite v4.11)
5. **Water Solubility:** 38.59 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.8616 (Henkel)
7. **Vapor Pressure:** 0.259 mm Hg at 20 °C (EPI Suite v4.0), 0.382 mm Hg at 25 °C (EPI Suite v4.11)
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 colorless liquid with a fresh, fruity, herbal, iris-note

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.3.10)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.20% (RIFM, 2020)
2. **Inhalation Exposure*: *:** 0.00028 mg/kg/day or 0.022 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.0042 mg/kg/day (RIFM, 2020)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. 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; B. Safford et al., 2015; B. Safford et al., 2024; B. 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 v4.5 (OECD, 2021b)
I	I	I

2. **Analogs Selected**:

a. **Genotoxicity:** Ethyl 2-methylpentanoate (CAS # 39255-32-8)
b. **Repeated Dose Toxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
c. **Reproductive Toxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1); Weight of Evidence (WoE) material: 2-ethylhexanoic acid (CAS # 149-57-5)
d. **Skin Sensitization:** Butyl 2-methylvalerate (CAS # 6297-41-2)
e. **Photoirritation/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 2-ethylhexanoate is not reported to occur in foods by the VCF*.
*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 (ECHA, 2017a); accessed on 06/15/23.

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 2-ethylhexanoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of ethyl 2-ethylhexanoate 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with ethyl 2-ethylhexanoate 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 (ECHA, 2017a). Under the conditions of the study, ethyl 2-ethylhexanoate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of ethyl 2-ethylhexanoate; however, read-across can be made to ethyl 2-methylpentanoate (CAS # 39255-32-8; see Section VI).

The clastogenicity of ethyl 2-methylpentanoate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with ethyl 2-methylpentanoate in DMSO at concentrations up to 1450 μg/mL in the dose range finding study; the main study was conducted at concentrations up to 1450 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2013b). Under the conditions of the study, ethyl 2-methylpentanoate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to ethyl 2-ethylhexanoate.

Based on the data available, ethyl 2-methylpentanoate does not present a concern for genotoxic potential, and this can be extended to ethyl 2-ethylhexanoate.

Additional References: RIFM, 1978.

Literature Search and Risk Assessment Completed On: 09/01/

23.

11.1.2. Repeated dose toxicity

The MOE for ethyl 2-ethylhexanoate 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 for ethyl 2-ethylhexanoate. Read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI) has sufficient 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, 2013a).

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 2-ethylhexanoate 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 2-ethylhexanoate, 333/0.0042 or 79286.

In addition, the total systemic exposure to ethyl 2-ethylhexanoate (4.2 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: 08/17/23.

11.1.3. Reproductive toxicity

The MOE for ethyl 2-ethylhexanoate 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 for ethyl 2-ethylhexanoate. Read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI) has sufficient 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. 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, 2013a).

In addition, ethyl 2-ethylhexanoate is expected to metabolize to 2-ethylhexanoic acid (CAS # 149-57-5; see Section VI), which was considered as a WoE material for this safety assessment. In a prenatal developmental toxicity study, 2-ethylhexanoic acid was administered to 25 Fischer 344 female rats/dose via oral gavage in corn oil at 0, 100, 250, or 500 mg/kg/day. Reduced fetal body weight was seen in the high-dose group. In addition, reduced skeletal ossification was observed in the mid- and high-dose groups. The NOAEL was considered to be 250 mg/kg/day. A similar study was conducted on 15 female New Zealand rabbits at 0, 25, 125, and 250 mg/kg/day. No developmental toxicity was observed in any dose groups and the NOAEL was considered to be 250 mg/kg/day, the highest dose tested. Another OECD 443 extended one-generation reproductive study was conducted in Wistar rats at 0, 80, 250, and 800 mg/kg/day (0, 1231, 3845, 12308 mg/kg) via diet. There were no adverse effects of the test material on fertility, developmental toxicity, and reproductive performance of F0- and F1-generation animals (ECHA, 2011).

Therefore, the ethyl 2-ethylhexanoate MOE for the reproductive toxicity endpoint can be calculated by dividing ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to ethyl 2-ethylhexanoate, 1000/0.0042 or 238095.

In addition, the total systemic exposure to ethyl 2-ethylhexanoate (4.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/17/23.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material butyl 2-methylvalerate, ethyl 2-ethylhexanoate presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for ethyl 2-ethylhexanoate. Therefore, butyl 2-methylvalerate (CAS # 6297-41-2; see Section VI) was used for the risk assessment of ethyl 2-ethylhexanoate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, ethyl 2-ethylhexanoate is not considered a skin sensitizer. Ethyl 2-ethylhexanoate and read-across material are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material butyl 2-methylvalerate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (RIFM, 2023b; RIFM, 2023a). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), and based on the 2 out of 3 Defined Approach, butyl 2-methylvalerate is a non-sensitizer. In a guinea pig maximization test, ethyl 2-ethylhexanoate did not lead to skin sensitization reactions (RIFM, 1977). In a human maximization test, no skin sensitization reactions were observed when ethyl 2-ethylhexanoate was tested at 8280 μg/cm^2 (RIFM, 1982).

Based on the WoE from structural analysis and *in vitro*, animal, and human studies on the read-across material as well as the target material, ethyl 2-ethylhexanoate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/03/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and *in vivo* study data, ethyl 2-ethylhexanoate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, ethyl 2-ethylhexanoate does not present a concern for photoallergenicity.

Table 1
Summary of existing data on Butyl 2-methylvalerate as read-across for Ethyl 2-ethylhexanoate.

	Human Data				Animal Data		
WoE Skin Sensitization Potency Category[1]	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT	Buehler
No evidence of sensitization[3]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	In vitro Data[2]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative	N/A		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021)..
[2]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table..
[3]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015)..

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In an *in vivo* photoirritation study, ethyl 2-ethylhexanoate was not photoirritating in mice (RIFM, 1976). Based on the *in vivo* study data and the lack of absorbance, ethyl 2-ethylhexanoate does not present a concern for photoirritation. Based on the lack of absorbance, ethyl 2-ethylhexanoate does not present a concern for 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 photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/11/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for ethyl 2-ethylhexanoate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are limited inhalation data available on ethyl 2-ethylhexanoate. Based on the Creme RIFM Model, the inhalation exposure is 0.022 mg/day. This exposure is 63.6 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, 1979.

Literature Search and Risk Assessment Completed On: 08/31/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl 2-ethylhexanoate 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 VoU 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 2-ethylhexanoate 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 2-ethylhexanoate 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, 2017b). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current VoU (2019), ethyl 2-ethylhexanoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation***:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. Ethyl 2-ethylhexanoate has been pre-registered for REACH with no additional data at this time.

11.2.2. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.7	3.7
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.00770 μg/L. The 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: 08/16/23.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 03/14/24.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	7.70			1000000	0.00770	

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114708.

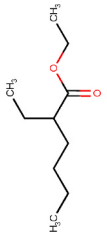
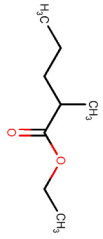
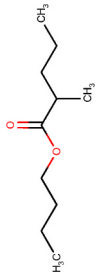
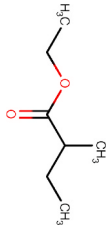
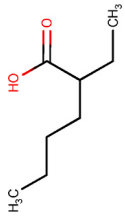
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in 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 Chemicals Agency read-across assessment framework (ECHA, 2017c).

- 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 v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- 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 v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material
Principal Name	Ethyl 2-ethylhexanoate	Ethyl 2-methylpentanoate	Butyl 2-methylvalerate	Ethyl 2-methylbutyrate	2-Ethylhexanoic acid
CAS No.	2983-37-1	39255-32-8	6297-41-2	7452-79-1	149-57-5
Structure					
Similarity (Tanimoto Score)		0.85	0.76	0.71	0.67
SMILES	CCCCC(CC)C(=O)OCC	CCCC(C)C(=O)OCC	CCCCOC(=O)C(C)CCC	CCOC(=O)C(C)CC	CCCCC(CC)C(O)=O
Endpoint		Genotoxicity (Clastogenicity)	Skin sensitization	Repeated dose toxicity Reproductive toxicity	Reproductive toxicity
Molecular Formula	$C_{10}H_{20}O_2$	$C_8H_{16}O_2$	$C_{10}H_{20}O_2$	$C_7H_{14}O_2$	$C_8H_{16}O_2$
Molecular Weight	172.268	144.214	172.268	130.187	144.214
Melting Point (°C, EPI Suite)	−20.47	−43.92	−20.47	−56.05	37.72
Boiling Point (°C, EPI Suite)	198.83	157.09	198.83	134.87	228.00

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.09E+01	3.84E+02	5.09E+01	1.07E+03	8.35E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.86E+01	3.57E+02	3.86E+01	1.07E+03	2.00E+03
Log KOW	3.74	2.76	3.74	2.26	2.64
J_{max} (μg/cm^2/h, SAM)	4.49	25.85	4.49	55.11	125.46
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.29E+02	7.33E+01	1.29E+02	5.52E+01	2.89E-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)	Structural alert for nongenotoxic carcinogenicity|Substituted n-alkylcarboxylic acids (Nongenotox)	Structural alert for nongenotoxic carcinogenicity|Substituted n-alkylcarboxylic acids (Nongenotox)			
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)	Sodium valproate (Renal toxicity) Alert|Valproic acid (Hepatotoxicity) Alert			Urethane (Renal toxicity) Alert	
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, non-cyclic structure			Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)			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 v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on ethyl 2-ethylhexanoate (CAS # 2983-37-1). 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, ethyl 2-methylpentanoate (CAS # 39255-32-8), butyl 2-methylvalerate (CAS # 6297-41-2), and ethyl 2-methylbutyrate (CAS # 7452-79-1) were identified as read-across analogs and 2-ethylhexanoic acid (CAS # 149-57-5) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 2-methylpentanoate (CAS # 39255-32-8) was used as a read-across analog for the target material, ethyl 2-ethylhexanoate (CAS # 2983-37-1), for the genotoxicity (clastogenicity) endpoint.
  - o The target material and the read-across analog are both aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target material contains longer carbon chains compared to the read-across analog. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of 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.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog contains an *in silico* alert for nongenotoxic carcinogenicity. The data from the genotoxicity (clastogenicity) sections confirms that the read-across analog is not genotoxic. Therefore, based on the structural similarity between the read-across analog and the target material and the data from the read-across analog. The predictions are superseded by the data.
  - 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.
- Butyl 2-methylvalerate (CAS # 6297-41-2) was used as a read-across analog for the target material, ethyl 2-ethylhexanoate (CAS # 2983-37-1), for the skin sensitization endpoint.
  - o The target material and the read-across analog are both aliphatic esters.
  - o The key difference between the target material and the read-across analog is that on the alcohol side of the ester, the carbon chain is longer for the read-across analog compared to the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog do not display *in silico* alerts for the skin sensitization endpoint. Data for the read-across analog indicates that it is not a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - 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.
- Ethyl 2-methylbutyrate (CAS # 7452-79-1) was used as a read-across analog for the target material, ethyl 2-ethylhexanoate (CAS # 2983-37-1), for the repeated dose toxicity and reproductive toxicity endpoints, and 2-ethylhexanoic acid (CAS # 149-57-5) was used as a WoE material for the reproductive toxicity endpoint.
  - o The target material and the read-across analog are both aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the read-across analog contains a shorter carbon chain length compared to the target material. Therefore, to satisfy the structural domain of the target material, 2-ethylhexanoic acid (CAS # 149-57-5) was used as a WoE material for the reproductive toxicity endpoint. This chemical is the acid metabolite of the target material and therefore contains the same carbon chain as the target. The read-across analog, combined with the WoE material, contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of 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.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog contain *in silico* alerts for urethane renal toxicity (repeated dose toxicity), non-binder, and non-toxicant (reproductive toxicity). However, the data from the repeated dose toxicity and reproductive toxicity sections confirm that the MOE for the target material is adequate under the current usage. Therefore, the predictions are superseded by the data.
  - 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.

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