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RIFM fragrance ingredient safety assessment, ethyl hexanoate, CAS Registry Number 123-66-0

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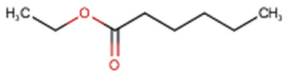

Abbreviation/Definition List:

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

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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., 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.,

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2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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, 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 hexanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that ethyl hexanoate is not genotoxic. Data on ethyl hexanoate provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data on ethyl hexanoate and read-across analog methyl octanoate (CAS # 111-11-5) provided ethyl hexanoate a No Expected Sensitization Induction Level (NESIL) of 4700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; ethyl hexanoate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog butyl propionate (CAS # 590-01-2). The environmental endpoints were evaluated; ethyl hexanoate 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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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2015f, RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM, (2017b)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	RIFM, (2017b)
Skin Sensitization: NESIL = 4700 μg/cm^2.	RIFM, (2018b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 1331.19 mg/m^3.	(Banton et al., 2000)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 79% (OECD 301F)	RIFM (2000)
Bioaccumulation: Screening-level: 34 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 4.492 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: 4.492 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.4492 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1	

1. Identification

1. **Chemical Name:** Ethyl hexanoate
2. **CAS Registry** Number**:** 123-66-0
3. **Synonyms:** Capronic ether absolute; Ethyl caproate; Hexanoic acid, ethyl ester; アルカン酸（C = 6 ~ 10）アルキル（C = 1 ~ 10）; Ethylcapronat; Ethyl hexanoate
4. **Molecular Formula:** $C_8H_{16}O_2$
5. **Molecular Weight:** 144.21
6. **RIFM Number:** 667
7. **Stereochemistry:** No isomeric center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 165 °C (Fragrance Materials Association [FMA] Database), 170.05 °C (EPI Suite), 167.3 °C at 1013 hPa (RIFM, 2015d)
2. **Flash Point:** 49 °C (Globally Harmonized System), 120 °F; CC (FMA Database), 44.5 °C (average corrected and rounded down to the nearest 0.5 °C) (RIFM, 2015b)
3. **Log K_{OW}:** log P_{ow} = 3.1 RIFM, 2011 (), 2.83 (EPI Suite), 2.96 at 22.4 °C (RIFM, 2015a)
4. **Melting Point**: −32.64 °C (EPI Suite), −68.3 °C at 1007–1014 hPa (RIFM, 2015d)
5. **Water Solubility:** 308.7 mg/L (EPI Suite)
6. **Specific Gravity:** 0.869–0.873 (FMA Database), 0.867–0.871 (FMA Database)
7. **Vapor Pressure:** 1.27 mm Hg at 20 °C (EPI Suite v4.0), 0.8 mm Hg 20 °C (FMA Database), 1.8 mm Hg at 25 °C (EPI Suite); 3.0 hPa at 20 °C, 4.0 hPa at 25 °C, and 15.0 hPa at 50 °C (RIFM, 2015c), 3–15 hPa at 20–50 °C (ECHA, 2017a)
8. **UV Spectra:** No significant 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 which has a powerful, diffusive, fruity-winey odor, suggestive of apple, banana, and pineapple with a slightly floral undertone

3. Volume of use (worldwide band)

1. 100–1000 metric tons (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.023% (RIFM, 2018a)
2. **Inhalation Exposure*:** 0.00048 mg/kg/day or 0.036 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.0020 mg/kg/day (RIFM, 2018a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey, 2015, 2017; Safford, 2015, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

6.1. *Cramer Classification: Class I, Low*

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

6.2. *Analogs Selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Methyl octanoate (CAS # 111-11-5)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Butyl propionate (CAS # 590-01-2)
g. **Environmental Toxicity:** None

6.3. *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 hexanoate is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*)	Banana (*Musa sapientum* L.)
Anise brandy	Bantu beer
Apple brandy	Beef

(*continued on next column*)

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Apple fresh (*Malus* species)	Beer
Apple processed (*Malus* species)	Bilberry wine
Apricot (*Prunus armeniaca* L.)	Black currants (*Ribes nigrum* L.)
Arrack	Blackberry brandy
Artocarpus species	Blue cheeses
Babaco fruit (*Carica pentagona Heilborn*)	Cape gooseberry (*Physalis peruviana* L.)
Capers (*Capparis spinoza*)	Grape (*Vitis* species)
Cashew apple (*Anacardium occidentale*)	Grape brandy
Cashew apple wine	Guava and feyoa
Ceriman, pinanona (*Monstera deliciosa* Liebm.)	Guava wine
Cheddar cheese	Hog plum (*Spondias mombins* L.)
Cheese, various types	Honey
Cherimoya (*Annona cherimolia* Mill.)	Kiwifruit (*Actinidia chinensis, syn. A. deliciosa*)
Cherry (*Prunus avium* [sweet], pr. Cerasus [sour])	Lamb and mutton
	Litchi (*Litchi chinensis* Sonn.)
Cherry brandy	Litchi wine
Chinese liquor (baiju)	Macadamia nut (*Macadamia integrifolia*)
Chinese quince (*Pseudocydonia sinensis* Schneid)	Maize (*Zea mays* L.)
Cider (Apple wine)	Mangifera species
Citrus fruits	Mastic (*Pistacia lentiscus*)
Cloudberry (*Rubus chamaemorus* L.)	Melon
Cloves (*Eugenia caryophyllata* Thunberg)	Mezcal (*Agave salmiana*)
Cocoa	Milk and milk products
Cupuacu (*Theobroma grandiflorum* Spreng.)	Miso (soybean, rice, or fish)
Date (*Phoenix dactylifera* L.)	Mountain papaya (*C. candamarcensis, C. pubescens)*
Durian (*Durio zibethinus*)	Mulberry spirit (*Mouro*)
Fig (*Ficus carica* L.)	Muruci (*Byrsonima crassifolia*)
Fish	Mushroom
Gabiroba (*Campomanesia xanthocarpa*)	Naranjilla fruit (*Solanum quitoense* Lam.)
Nectarine	Rum
Noni (*Morinda citrifolia* L.)	Rye bread
Olive (*Olea europaea*)	Sake
Passion fruit (*Passiflora* species)	Sea buckthorn (*Hippophaë rhamnoides* L.)
Passion fruit wine	Sherry
Pawpaw (*Asimina triloba* Dunal.)	Soursop (*Annona muricata* L.)
Pear (*Pyrus communis* L.)	Spineless monkey orange (*Strychnos madagasc.*)
Pear brandy	Starfruit (*Averrhoa carambola* L.)
Peas (*Pisum sativum* L.)	Strawberry (*Fragaria* species)
Pineapple (*Ananas comosus*)	Strawberry wine
Plum (*Prunus* species)	Sugar molasses
Plum brandy	Swiss cheeses
Plum wine	Tapereba, caja fruit (*Spondias lutea* L.)
Pomegranate juice (*Punica granatum* L.)	Tequila (*Agave tequilana*)
Pomegranate wine (*Punica granatum* L.)	Tomato (*Lycopersicon esculentum* Mill.)
Pork	Truffle
Prickly pear (*Opuntia ficus indica*)	Vanilla
Quince, marmelo (*Cydonia oblonga* Mill.)	Vinegar
Rambutan (*Nephelium lappaceum* L.)	Whisky
Raspberry brandy	Wine
Raspberry, blackberry, and boysenberry	Wood apple (*Feronia limonia*)
Rice (*Oryza sativa* L.)	

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

9. REACH dossier

Available; accessed 01/04/21 (ECHA, 2017a).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for ethyl hexanoate 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)	0.36
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	1.6
4	Products related to fine fragrances	2.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.51
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.51
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.51
5D	Baby cream, oil, talc	0.17
6	Products with oral and lip exposure	1.2
7	Products applied to the hair with some hand contact	3.3
8	Products with significant ano-genital exposure (tampon)	0.17
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	8.1
10B	Aerosol air freshener	14
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.17
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 ethyl hexanoate, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 4700 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).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, ethyl hexanoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of ethyl hexanoate 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 *Escherichia coli* WP2uvrA were treated with ethyl hexanoate 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, 2015f). Under the conditions of the study, ethyl hexanoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl hexanoate 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 ethyl hexanoate in DMSO at concentrations up to 824 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 20 h. Ethyl hexanoate did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, ethyl hexanoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2015e.

Literature Search and Risk Assessment Completed On: 12/07/20.

11.1.2. Repeated dose toxicity

The MOE for ethyl hexanoate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient data on ethyl hexanoate that can be used to support the repeated dose toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered test material ethyl hexanoate (ethyl caproate) at doses of 0, 100, 300, or 1000 mg/kg/day via oral gavage. Males were dosed for at least 50 days (2 weeks prior to mating and continued through the day before euthanasia), while females were dosed for 2 weeks prior to mating and continued through lactation day (LD) 13. Additional animals (6 rats/sex/group) in the control and high-dose recovery groups received ethyl caproate but were not mated; they were assigned to a 2-week period of recovery. One female in the control group was euthanized on LD 3 because all pups were found expired. This was considered to be incidental since it was observed in the control group and there were no clinical signs of toxicity. At 1000 mg/kg/day, statistically significant increased prothrombin time in both sexes and statistically significant increased kidney weights in females were observed. Furthermore, statistically significant decreases in gamma glutamyl transpeptidase were observed in all treatment group males. A statistically significant increase in thyroid hormone (T4) was observed in adult males and pups of the highest-dose group. Since there were no correlated microscopic findings associated with any of the alterations observed in the highest-dose group, these findings were not considered to be toxicologically relevant. Reversibility was also observed in the high-dose animals after the recovery period. Thus, the NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2017b; also available at ECHA, 2017a).

A default uncertainty factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The uncertainty factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the ethyl hexanoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl hexanoate NOAEL in mg/kg/day by the total systemic exposure to ethyl hexanoate, 333/0.0020, i.e., 166500.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for ethyl hexanoate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

In addition, the total systemic exposure to ethyl hexanoate (2.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of

use.

Deriv>ation of reference dose (RfD):

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, 2020b) and a reference dose of 3.33 mg/kg/day.

The reference dose for ethyl hexanoate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 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: 11/25/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient data on ethyl hexanoate that can be used to support the reproductive toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity with a reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered test material ethyl hexanoate (ethyl caproate) at doses of 0, 100, 300, or 1000 mg/kg/day via oral gavage. Males were dosed for at least 50 days (2 weeks prior to mating and continued through the day before euthanasia), while females were dosed for 2 weeks prior to mating and continued through LD 13. Additional animals (6 rats/sex/group) in the control and high-dose recovery groups received ethyl caproate but were not mated; they were assigned to a 2-week recovery period. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. One female in the control group was euthanized on LD 3 because all pups were found expired. This was considered to be incidental since it was observed in the control group and there were no clinical signs of toxicity. Non-parturition was also observed in 1 female each at the 100, 300, and 1000 mg/kg/day dose groups; these dams were euthanized on gestation day 28. This was considered incidental since there were no treatment-related macroscopic or microscopic findings. A statistically significant increase in thyroid hormone (T4) was observed in adult males (1.14-fold of control) and pups (1.20-fold of control) of the highest-dose group. Since there were no correlated changes in other parameters, including microscopic findings in thyroids (with parathyroids), this was not considered to be toxicologically relevant. No treatment-related adverse effects were observed in the estrous cycle, pre-coital time, fertility data, reproductive and littering findings, clinical signs, body weight, anogenital distance, nipple retention, or external examination of pups. Thus, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2017b; also available at ECHA, 2017a). Therefore, the ethyl hexanoate MOE for the reproductive toxicity endpoint can be calculated by dividing the ethyl hexanoate NOAEL in mg/kg/day by the total systemic exposure to ethyl hexanoate, 1000/0.002, i.e., 500000.

In addition, the total systemic exposure to ethyl hexanoate (2.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/07/20.

11.1.4. Skin sensitization

Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5), ethyl hexanoate is considered a skin sensitizer with a defined NESIL of 4700 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for ethyl hexanoate. Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5; see Section VI), ethyl hexanoate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Ethyl hexanoate was found to be negative in an *in chemico* direct peptide reactivity assay (DPRA) and *in vitro* LuSens assay and positive in the human cell line activation test (h-CLAT) (RIFM, 2015g). In a local lymph node assay (LLNA), read-across material methyl octanoate was found to be sensitizing with an EC3 value of 19.6% (4900 μg/cm^2) based on linear regression (RIFM, 2002). In a human maximization test, no skin sensitization reactions were observed with ethyl hexanoate when tested at 4% (2760 μg/cm^2) in petrolatum (RIFM, 1975). Additionally, in a confirmation of no induction in humans test (CNIH) with 4724 μg/cm^2 of read-across material methyl octanoate in 1:3 ethanol:diethyl phthalate (1:3 EtOH:DEP), no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2018b).

Based on the available data on read-across material methyl octanoate, summarized in Table 1, ethyl hexanoate is considered to be a weak skin sensitizer with a defined NESIL of 4700 μg/cm^2. 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. (Api, 2020b) and a reference dose of 3.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl hexanoate 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 hexanoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, Ethyl hexanoate does not present a concern for phototoxicity or photoallergenicity.

UV Spectra Analysis: UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the

Table 1
Data Summary for ethyl hexanoate as read-across material for methyl octanoate.

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
4900 [1]	Weak	4724	2760	NA	4700

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.

[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).

[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.

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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/04/20.

11.1.6. Local Respiratory Toxicity

There are no inhalation data available on ethyl hexanoate; however, in a 13-week, subchronic inhalation exposure study for the read-across analog butyl propionate (CAS # 590-01-2; see Section VI), a NOAEC of 684.19 mg/m^3 was reported (Banton, 2000; Ulrich, 2000).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery.

In a 13-week inhalation exposure study, Sprague Dawley rats (15/sex/group) were exposed to butyl propionate via whole-body inhalation for 6 h/day, 5 days/week (Banton, 2000; Ulrich, 2000). The treatment groups consisted of sham-exposed control (filtered air), 1331.19 mg/m^3, 3993.56 mg/m^3, and 7987.12 mg/m^3. All the animals were subjected to complete necropsy, including microscopic examination of lungs, nasal tissues, and trachea. Nasal tissues were microscopically evaluated at 6 different levels. Exposure-related effects were observed in the nasal tissues of the rats from the 3993.56 mg/m^3 and 7987.12 mg/m^3 groups. The effects exhibited degenerative changes to the nasal cavity olfactory epithelium consisting of vacuolation, cell necrosis, and mucosal atrophy at levels 3, 4, 5, and 6. The most pronounced effects were observed at levels 3 and 4. The lowest exposure group nasal tissue microscopy was comparable to the controls and did not show any nasal cavity tissue-related degenerative effects. Minimal vacuolation was observed in the control and the lowest exposure groups, which were different in appearance from the 3993.56 mg/m^3 and 7987.12 mg/m^3 groups and were therefore considered to be an artifact of the sub-optimal fixation of the epithelium. Based on the histopathologic observations in the nasal passages of rats exposed to control, 1331.19 mg/m^3, 3993.56 mg/m^3, and 7987.12 mg/m^3, the NOAEC was identified as 1331.19 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (1331.19 mg/m^3) × (1m^3/1000L) = 1.33 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (1.33 mg/L) × (61.2 L/day) = 81.4 mg/day
- (81.4 mg/day)/(0.0016 kg lung weight of rat*) = 50,875 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.036 mg/day; this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; and Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.055 mg/kg lung weight/day resulting in a MOE of 925000 (i.e., [50875 mg/kg lung weight/day]/[0.055 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.036 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/18.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl hexanoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers 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 hexanoate 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 ethyl hexanoate 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, 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). 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 hexanoate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation:**

RIFM, 1999: The biodegradability of the test material was determined using the closed bottle test according to the OECD 301D method. Under the conditions of the study, biodegradation of 50% was observed after 28 days.

RIFM, 2000: The ready biodegradability of the test material was evaluated using the manometric respiratory test according to the OECD 301F method. Under the conditions of the study, the test material showed a biodegradability of 79% after 28 days.

Ecotoxicity:

RIFM, 1999: A *Daphnia magna* acute toxicity study was conducted according to the 92/69 EEC C.2 method under static conditions. The

geometric mean of EC0/EC100 was reported to be 31 mg/L.

RIFM, 2017a: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h ErC50* (growth) and EyC50** (yield) were reported to be 11.8 mg/L, and 9.97 mg/L, based on time-weighted average mean measured concentrations.

RIFM, 2017c: A Fish (*Danio rerio*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50, based on measured concentrations, was reported to be 6.74 mg/L.

*Concentration of the test material with 50% inhibition effects related to growth rate inhibition when compared to the control.

**Concentration of the test material with 50% inhibition effects related to yield inhibition when compared to the control.

Other available data:

Ethyl hexanoate has been registered under REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since ethyl hexanoate 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.1	3.1
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on read-across, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.4492 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: 12/08/20.

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 04/17/21.

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. 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	21.44			1000000	0.02144	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	6.327	12.03	4.492	10000	0.4492	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	21.35	13.08	13.37			Neutral Organics

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.2021.112532.

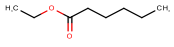
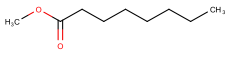
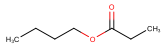
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow 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 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	
Principal Name	Ethyl hexanoate	Methyl octanoate	Butyl propionate
CAS No.	123-66-0	111-11-5	590-01-2
Structure			
Similarity (Tanimoto Score)		0.75	0.8
Read-across Endpoint		• Skin sensitization	• Respiratory toxicity
Molecular Formula	$C_8H_{16}O_2$	$C_9H_{18}O_2$	$C_7H_{14}O_2$
Molecular Weight	144.21	158.24	130.19
Melting Point (°C, EPI Suite)	−32.64	−20.94	−44.60
Boiling Point (°C, EPI Suite)	170.05	190.83	148.37
Vapor Pressure (Pa @ 25°C, EPI Suite)	240	68.4	620
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	2.83	3.32	2.34
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	629	64.4	925.9
J_{max} (mg/cm^2/h, SAM)	36.394	5.586	59.9
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	7.33E+001	9.73E+001	5.52E+001
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 alert found	• No alert found	
Local Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• 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

Summary

There are insufficient toxicity data on ethyl hexanoate (CAS # 123-66-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, methyl octanoate (CAS # 111-11-5) and butyl propionate (CAS # 590-01-2) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Methyl octanoate (CAS # 111-11-5) was used as a read-across analog for the target material ethyl hexanoate (CAS # 123-66-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target material is a hexanoate ethyl ester, whereas the read-across analog is an octanoate methyl ester. 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 material.
  - 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 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 do not have alerts of toxicity. The data described in the skin sensitization section confirm that the read-across analog is a weak sensitizer. The *in silico* alerts are inconsistent with data and are superseded by the data for skin sensitization.
  - 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.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Butyl propionate (CAS # 590-01-2) was used as a read-across analog for the target material ethyl hexanoate (CAS # 123-66-0) for the local respiratory endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target material is a hexanoate ester, whereas the read-across analog is a propionate ester. 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 material.
  - 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 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 do not have alerts of toxicity. The data described in the skin sensitization section confirm that the read-across analog is a weak sensitizer. The *in silico* alerts are inconsistent with data and are superseded by the data for skin sensitization.
  - 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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