Food and Chemical Toxicology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, ethyl heptanoate, CAS Registry Number 106-30-9

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

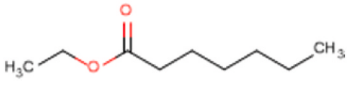
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 062921. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Ethyl heptanoate
CAS Registry Number: 106-30-9



(*continued on next column*)

(*continued*)

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 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., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

(*continued on next page*)

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2021.112501
Received 21 April 2021; Received in revised form 29 June 2021; Accepted 7 August 2021
Available online 10 August 2021

(*continued*)

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 heptanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from ethyl heptanoate and read-across analog ethyl hexanoate (CAS # 123-66-0) show that ethyl heptanoate is not expected to be genotoxic. Data on analog ethyl hexanoate (CAS # 123-66-0) provide a calculated margin of exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data on ethyl heptanoate and analog methyl octanoate (CAS # 111-11-5) provided ethyl heptanoate 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 heptanoate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the analog butyl propionate (CAS # 590-01-2). The environmental endpoints were evaluated; ethyl heptanoate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

(*continued on next column*)

(*continued*)

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2015b; RIFM, 2016c)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (2017a)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	RIFM (2017a)
Skin Sensitization: NESIL = 4700 μg/cm^2.	RIFM (2018a)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 1331.19 mg/m^3.	Banton (2000)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 73% (OECD 301F)	RIFM (1998a)
Bioaccumulation: Screening-level: 72 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 2.235 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: 2.235 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.2235 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1	

1. Identification

1. **Chemical Name:** Ethyl heptanoate
2. **CAS Registry Number:** 106-30-9
3. **Synonyms:** Cognac oil, artificial; Enanthic ether; Ethyl enantate; Ethyl heptoate; Ethyl heptylate; Ethyl oenanthate; Heptanoic acid, ethyl ester; Oenanthic ether; 脂肪酸(C = 6~10)ｱﾙｷﾙ(C = 1~10)ｴｽﾃﾙ; Ethylheptylat; Ethyl heptanoate
4. **Molecular Formula:** $C_9H_{18}O_2$
5. **Molecular Weight:** 158.24
6. **RIFM Number:** 685
7. **Stereochemistry:** No isomeric center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 188 °C (Fragrance Materials Association [FMA Database]), 190.83 °C (EPI Suite)
2. **Flash Point:** 57 °C (Globally Harmonized System), 135 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.0 at 35 °C (RIFM, 1998b), 3.32 (EPI Suite)
4. **Melting Point:** −20.94 °C (EPI Suite)
5. **Water Solubility:** 101.9 mg/L (EPI Suite), 126 mg/L at 20 ± 0.5 °C, pH 6.1 (RIFM, 2016b)
6. **Specific Gravity:** 0.867–0.872 (FMA Database), 0.869–0.874 (FMA Database)
7. **Vapor Pressure:** 0.473 mm Hg at 20 °C (EPI Suite v4.0), 0.3 mm Hg at 20 °C (FMA Database), 0.686 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless to pale yellow liquid with fruity, wine-like odor and taste; burning aftertaste with brandy odor

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.015% (RIFM, 2018b)
2. **Inhalation Exposure*:** 0.00078 mg/kg/day or 0.057 mg/day (RIFM, 2018b)
3. **Total Systemic Exposure**:** 0.0019 mg/kg/day (RIFM, 2018b)

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

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
a. **Genotoxicity:** Ethyl hexanoate (CAS # 123-66-0)
b. **Repeated Dose Toxicity:** Ethyl hexanoate (CAS # 123-66-0)
c. **Reproductive Toxicity:** Ethyl hexanoate (CAS # 123-66-0)
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
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

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

Acerola (*Malpighia*)	Beer
Apple brandy	Bilberry wine
Apple fresh (*Malus* species)	Cashew Apple (*Anacardium occidentale*)
Apricot (*Prunus armeniaca* L.)	Ceriman, pinanona (*Monstera deliciosa* Liebm.)

(continued on next column)

(continued)

Bantu beer	Cheese, various types
Chinese liquor (baijiu)	Passion fruit wine
Cider (apple wine)	Pear brandy
Citrus fruits	Peas (*Pisum sativum* L.)
Cocoa	Pineapple (*Ananas comosus*)
Date (*Phoenix dactylifera* L.)	Plum (*Prunus species*)
Durian (*Durio zibethinus*)	Plum brandy
Filbert, hazelnut (*Corylus avellano*)	Prickly pear (*Opuntia ficus indica*)
Fish	Quince, marmelo (*Cydonia oblonga* Mill.)
Grape (*Vitis* species)	Rice (*Oryza sativa* L.)
Grape brandy	Rum
Hop (*Humulous lupulus*)	Sake
Macadamia nut (*Macadamia integrifolia*)	Sherry
Maize (*Zea mays* L.)	Spineless monkey orange (*Strychnos madagasc.*)
Melon	Starfruit (*Averrhoa carambola* L.)
Milk and milk products	Strawberry (Fragaria species)
Miso (soybean, rice, or fish)	Strawberry wine
Mountain papaya (*C. candamarcensis, C. pubescens*)	Tequila (*Agave tequilana*)
Nectarine	Vinegar
Olive (*Olea europaea*)	Whiskey
Passion fruit (*Passiflora* species)	Wine

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

9. REACH dossier

Available; accessed on 01/05/21 (ECHA, 2016).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for ethyl heptanoate 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	2.2
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	2.6
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)	7.9
10B	Aerosol air freshener	14
11		0.17

(continued on next page)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	
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 heptanoate, 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 heptanoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of ethyl heptanoate 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, 2016a). Under the conditions of the study, ethyl octanoate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of ethyl heptanoate; however, read-across can be made to ethyl hexanoate (CAS # 123-66-0; see Section VI). 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 metabolic activation (S9) for 4 h and in the absence of metabolic activation for 20 h. Ethyl hexanoate did not increase the frequency of binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2016c). 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 octanoate does not present a concern for genotoxic potential.

Additional References: RIFM, 2015a.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are limited repeated dose toxicity data on ethyl heptanoate. A subchronic toxicity study was conducted on weanling Osborne-Mendel rats. Groups of 10 rats/sex/dose were fed diets containing test material, ethyl heptanoate, at dose levels of 0, 1000, or 10000 ppm for 13 weeks. No treatment-related changes were reported on growth, hematological parameters, and histopathology at any dose level. Thus, the NOAEL was considered to be 10000 ppm (equivalent to 500 mg/kg/day, as per the conversion factors for old rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives), the highest dose tested (Hagan, 1967).

Read-across material ethyl hexanoate (CAS # 123-66-0; see Section VI) has an OECD 422/GLP combined repeated dose toxicity with reproduction/developmental toxicity screening test 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 dead. 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, 2017a; ECHA, 2017a).

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*.

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

Data from the target material was from a non-guideline study with only 2 dose levels; thus, the NOAEL from the more robust OECD 422 study for a read-across material was selected for this safety assessment.

Therefore, the ethyl heptanoate 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 heptanoate, 333/0.0019 or 175263.

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.

In addition, the total systemic exposure to ethyl heptanoate (1.9 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.

Derivation 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 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 reference dose for ethyl heptanoate 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: Bar (1967).

Literature Search and Risk Assessment Completed On: 11/25/20.

11.1.3. Reproductive Toxicity

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

11.1.3.1. Risk Assessment. There are insufficient reproductive toxicity data on ethyl heptanoate. Read-across material ethyl hexanoate (CAS # 123-66-0; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive 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 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 dead. 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 in the 100, 300, and 1000 mg/kg/day dose groups; these dams were euthanized on GD 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 thyroid glands (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, 2017a; also available in ECHA, 2017a). **Therefore, the ethyl heptanoate 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 heptanoate, 1000/0.0019, or 526316.**

In addition, the total systemic exposure to ethyl heptanoate (1.9 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 heptanoate 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 heptanoate. Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5; see Section VI), ethyl heptanoate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 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 2 separate human maximization tests, no skin sensitization reactions were observed with ethyl heptanoate when tested at 4% (2760 μg/cm^2) and 8% (5520 μg/cm^2) in petrolatum (RIFM, 1976; RIFM, 1975). Additionally, in a confirmatory Confirmation of No Induction in Humans (CNIH) with 4724 μg/cm^2 of 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, 2018a).

Based on the available data on read-across material methyl octanoate, summarized in Table 1, ethyl heptanoate 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. (RIFM, 2020b) and a reference dose of 3.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/29/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, ethyl heptanoate 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 heptanoate 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 heptanoate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 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 heptanoate; however, in a 13-week, subchronic inhalation exposure study for the analog butyl propionate (CAS # 590-01-2; see Section VI), a NOAEC of 684.19 mg/m^3

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

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	5520	NA	4700

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

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 rats from the 3993.56 mg/m^3 and 7987.12 mg/m^3 groups; there were 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 group, 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 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*) = 50875 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.057 mg/day; this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; 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 0.088 mg/kg lung weight/day resulting in an MOE of 578125 (i.e., [50875 mg/kg lung weight/day]/[0.088 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 0.057 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 heptanoate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material’s regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, ethyl heptanoate 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 is > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl heptanoate 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 heptanoate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1998a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F guidelines. After 28 days, biodegradation of 73% was observed.

RIFM, 1999: The biodegradability of the test material was determined using the closed bottle test according to the OECD 301D method. Biodegradation of 67% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. RIFM, 1999: A *Daphnia magna* immobilization test was conducted according to the 92/69/EEC method C.2 guidelines under static conditions. The 48-h EC0 was reported to be > 26.3 mg/L (arithmetic mean of analytical values).

RIFM, 2016d: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 values based on time-weighted average concentration for inhibition of growth rate (ErC50) and yield (EyC50) were reported to be 0.440 mg/L and 0.202 mg/L, respectively.

RIFM, 2017b: A fish (Zebrafish) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 value based on geometric mean measured concentration was reported to be greater than 1.01 mg/L.

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

11.2.3. 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.

*read-across.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.0	4.0
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 available data, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.2235 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 Volume of Use.

Literature Search and Risk Assessment Completed On: 12/09/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112501.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.874			1000000	0.003874	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	3.587	6.474	2.235	10000	0.2235	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	8.486	5.443	6710			Neutral Organics

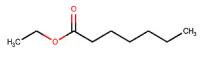
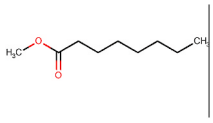
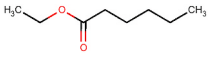
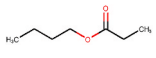
Appendix

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		
Principal Name	Ethyl heptanoate	Methyl octanoate	Ethyl hexanoate	Butyl propionate
CAS No.	106-30-9	111-11-5	123-66-0	590-01-2
Structure				
Similarity (Tanimoto Score)		0.89	0.93	0.55
Read-across Endpoint		• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity • Genotoxicity	• Local respiratory toxicity
Molecular Formula	$C_9H_{18}O_2$	$C_9H_{18}O_2$	$C_8H_{16}O_2$	$C_7H_{14}O_2$
Molecular Weight	158.24	158.24	144.21	130.19
Melting Point (°C, EPI Suite)	−20.94	−20.94	−32.64	−44.60
Boiling Point (°C, EPI Suite)	190.83	190.83	170.05	148.37
Vapor Pressure (Pa @ 25°C, EPI Suite)	91.5	68.4	240	620
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.32	3.32	2.83	2.34
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	101.9	64.4	629	925.9
J_{max} (μg/cm^2/h, SAM)	22.75	5.586	36.394	59.9
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.06E+001	9.73E+001	7.33E+001	5.52E+001
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found		No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found		No alert found	
Carcinogenicity (ISS)	No alert found		No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found		No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found		No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found		No alert found	
Oncologic Classification	Not classified		Not classified	
Repeated Dose				
Repeated Dose (HESS)	Not categorized		Urethane (Renal toxicity) Alert	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Toxicant (good 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)		

(*continued on next page*)

(*continued*)

	Target Material	Read-across		
Principal Name	Ethyl heptanoate	Methyl octanoate	Ethyl hexanoate	Butyl propionate
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		
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on ethyl heptanoate (CAS # 106-30-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties, and expert judgment, methyl octanoate (CAS # 111-11-5), ethyl hexanoate (CAS # 123-66-0), 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 heptanoate (CAS # 106-30-9) 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 is a heptanoate ester, whereas the read-across analog is an octanoate 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 a 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 confirms 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.
- Ethyl hexanoate (CAS # 123-66-0) was used as a read-across analog for the target material ethyl heptanoate (CAS # 106-30-9) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - 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 heptanoate ester, whereas the read-across analog is a hexanoate 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 a 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 for toxicity. Data are consistent with the *in silico* alerts.
  - 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 propionate (CAS # 590-01-2) was used as a read-across analog for the target material ethyl heptanoate (CAS # 106-30-9) 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 is a hexanoate ethyl ester, whereas the read-across analog is a propionate butyl 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 a 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 the skin sensitization endpoint.
- 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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Banton, M.I., Tyler, T.R., Ulrich, C.E., Nemec, M.D., Garman, R.H., 2000. Subchronic and developmental toxicity studies of n-butyl propionate vapor in rats. J. Toxicol. Environ. Health, Part A. 61 (2), 79–105.

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel Fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizin Ernahr 8, 244–251.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., et al., 2010, July. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (S1), S4. Springer International Publishing.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Echa, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

Echa, 2016. Registration Dossier Ethyl Enantate. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/16702/1/2.

Echa, 2017a. Registration Dossier Ethyl Hexanoate. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/21457/1.

Echa, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Chem. Toxicol. 5 (2), 141–157.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

Ifra (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance Skin Sensitization Evaluation and Human Testing, Dermatitis. https://doi.org/10.1097/DER.0000000000000684. November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from.

Oecd, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

Oecd, 2018. The OECD QSAR Toolbox v3.2–v4.2. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1799. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1976. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1797. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1998a. Ready Biodegradability of Ethyl Heptanoate (Ethyl Oenanthate). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51232.

RIFM (Research Institute for Fragrance Materials, Inc.), 1998b. Partition Coefficient N-Octanol/water of Ethyl Heptanoate (Ethyl Oenanthate). Unpublished Report from Givaudan. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 51233.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Investigation of the Ecological Properties of Ethyl Heptanoate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 57385.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Methyl Octanoate: Murine Lymph Node Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 42131.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Ethyl Hexanoate (Ethylcapronat): Gene Mutation Assay in Chinese Hamster V79 Cells in Vitro (V79/HPRT). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 70287.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Ethyl Hexanoate (Ethylcapronat): Salmonella typhimurium and Escherichia coli Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 70288.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Ethyl Heptanoate: Salmonella typhimurium and Escherichia coli Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 70313.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Ethyl Heptanoate (Ethylheptylat): Water Solubility. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71086.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016c. Ethyl Hexanoate (Ethylcapronat): Micronucleus Test in Human Lymphocytes in Vitro. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71103.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016d. Ethyl Heptanoate: Alga, Growth Inhibition Test with Pseudokirchneriella Subcapitata, 72 Hours. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 71309.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017a. Ethyl Hexanoate (Ethylcapronat): Combined Repeated Dose Oral Gavage Toxicity Study with the Reproduction/developmental Toxicity Screening in Sprague-Dawley Rats. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 72645.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. Ethyl Heptanoate (Ethylheptylat): Fish (Zebrafish), Acute Toxicity Test, Semi-static, 96 Hours. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 72817.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018a. Methyl Octanoate: Repeated Insult Patch Test (RIPT). RIFM Report Number 73322. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018b. Exposure Survey 22. November 2018.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76272.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Cronin, M.T. D., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.

Ulrich, C.E., Nemec, M.D., Banton, M.I., Tyler, T.R., Garmon, R.H., 2000. Subchronic and developmental toxicity studies of n-butyl propionate vapor in rats. Toxicologist 54 (1), 292.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.