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 octanoate, CAS Registry Number 106-32-1

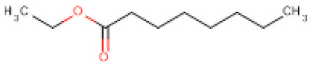
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], 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] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, 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] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, 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] *Member of Expert Panel, 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] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, 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: 041721. 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.



(*continued on next column*)

(*continued*)

Name: Ethyl octanoate CAS Registry Number: 106-32-1

Abbreviation/Definition List:

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

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2021.112500
Received 21 April 2021; Received in revised form 30 July 2021; Accepted 7 August 2021
Available online 11 August 2021

(*continued*)

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; Safford et al., 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 et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Ethyl octanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on ethyl octanoate and read-across analog ethyl hexanoate (CAS # 123-66-0) show that ethyl octanoate is not expected to be genotoxic. Data on ethyl octanate and analog ethyl hexanoate (CAS # 123-66-0) provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoint. Data on ethyl octanoate and analog methyl octanoate (CAS # 111-11-5) provided ethyl octanoate a NESIL of 4700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; ethyl octanoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to ethyl octanoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; ethyl octanoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2016b; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. RIFM (2017c)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day. RIFM (2017c)
Skin Sensitization: NESIL = 4700 μg/cm^2. RIFM (2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 91% (OECD 301B) RIFM (2002c)
Bioaccumulation: Screening-level: 151 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 1.104 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 et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 1.104 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1104 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name**: Ethyl octanoate
2. **CAS Registry Number**: 106-32-1
3. **Synonyms**: Ethyl caprylate; Ethyl octoate; Ethyl octylate; Octanoic acid, ethyl ester; 脂肪酸(C = 6–10)ｱﾙｷﾙ(C = 1–10)ｴｽﾃﾙ; Ethyl-caprylat; Ethyl octanoate
4. **Molecular Formula**: $C_{10}H_{20}O_2$
5. **Molecular Weight**: 172.27 g/mol
6. **RIFM Number**: 716
7. **Stereochemistry**: No isomeric center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 208 °C (Fragrance Materials Association [FMA]), 210.7 °C (EPI Suite)
2. **Flash Point:** 175 °F; CC (FMA), 79 °C (Globally Harmonized System)
3. **Log K_{ow}:** 3.81 (EPI Suite)
4. **Melting Point**: −9.5 °C (EPI Suite)
5. **Water Solubility:** 33.39 mg/L (EPI Suite)
6. **Specific Gravity:** 0.865–0.869 (FMA), 0.867–0.871 (FMA)
7. **Vapor Pressure:** 0.158 mm Hg at 20 °C (EPI Suite v4.0), 0.2 mm Hg at 20 °C (FMA), 0.235 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 colorless oily liquid with a sweet-winey-fruity odor of great tenacity and a fruity-winey, sweet odor reminiscent of apricot, banana, and pineapple with a “fermented"-winey note and a sweet-winey-brandy-like taste with a distinct fruity note (Arctander, 1969)

3. Volume of Use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance**: 0.0044% (RIFM, 2017d)
2. **Inhalation Exposure***: 0.00028 mg/kg/day or 0.022 mg/day (RIFM, 2017d)
3. **Total Systemic Exposure****: 0.0010 mg/kg/day (RIFM, 2017d)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. *Cramer Classification: Class I, Low*

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

6.2. *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:** None
g. **Environmental Toxicity:** None

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

Acerola (*Malpighia*)	Black currants (*Ribes nigrum* L.)
Anise brandy	Blackberry brandy
Apple brandy (*Calvados*)	Blue cheeses
Apple fresh (*Malus* species)	Buckwheat
Apple processed (*Malus* species)	Cape gooseberry (*Physalis peruviana* L.)
Apricot (*Prunus armeniaca* L.)	Capers (*Capparis spinoza*)
Arrack	*Capsicum* species
Babaco fruit (*Carica pentagona* Heilborn)	Cashew apple (*Anacardium occidentale*)
Banana (*Musa sapientum* L.)	Cashew apple wine
Bantu beer	Cashew nut (*Anacardium occidentale*)
Beer	Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Bilberry wine	Cheddar cheese
Cheese, various types	Kiwifruit (*Actinidia chinensis,* syn. *A. Deliciosa*)
Cherimoya (*Annona cherimolia* Mill.)	Litchi (*Litchi chinensis* Sonn.)
Cherry (*Prunus avium* [sweet], *Pr. cerasus* [sour])	Litchi wine
Cherry brandy	Macadamia nut (*Macadamia integrifolia*)
Chinese liquor (baijiu)	*Mangifera* species
Chinese quince (*Pseudocydonia sinensis* Schneid)	Mastic (*Pistacia lentiscus*)
Cider (apple wine)	Melon
Citrus fruits	Mezcal (*Agave salmiana*)
Cloves (*Eugenia caryophyllata* Thunberg)	Milk and milk products
Cocoa category	Miso (soy bean, rice, or fish)
Coconut (*Cocos nucifera* L.)	Mountain papaya (*C. candamarcensis, C. pubescens*)
Dalieb, palmyra palm fruit (*Borassus aethiopum* L.)	Mulberry spirit (*Mouro*)
Date (*Phoenix dactylifera* L.)	Muruci (*Byrsonima crassifolia*)
Durian (*Durio zibethinus*)	Mustard (*Brassica* species)
Fish	Naranjilla fruit (*Solanum quitoense* Lam.)
Grape (*Vitis* species)	Nectarine
Grape brandy	Noni (*Morinda citrifolia* L.)
Guava and feyoa	Olive (*Olea europaea*)
Guava wine	Papaya (*Carica papaya* L.)
Hog plum (*Spondias mombins* L.)	Passion fruit (*Passiflora* species)
Honey	Passion fruit wine
Pear (*Pyrus communis* L.)	Pawpaw (*Asimina triloba* Dunal.)
Pear brandy	Peach (*Prunus persica* L.)
Peas (*Pisum sativum* L.)	Sherry
Pineapple (*Ananas comosus*)	Soursop (*Annona muricata* L.)
Plum (*Prunus* species)	Spineless monkey orange (*Strychnos madagasc.*)
Plum brandy	Starfruit (*Averrhoa carambola* L.)
Plum wine	Strawberry (*Fragaria* species)
Pomegranate juice (*Punica granatum* L.)	Strawberry wine
Pomegranate wine (*Punica granatum* L.)	Sugar molasses
Pork	Swiss cheeses
Prickly pear (*Opuntia ficus indica*)	Tamarind (*Tamarindus indica* L.)
Quince, marmelo (*Cydonia oblonga* Mill.)	Tapereba, caja fruit (*Spondias lutea* L.)
Raspberry brandy	Tea
Raspberry, blackberry, and boysenberry	Tequila (*Agave tequilana*)
Rice (*Oryza sativa* L.)	Truffle
Rum	Vinegar
Sake	Wheaten bread
Sea buckthorn (*Hippophaë rhamnoides* L.)	Whisky
	Wine

(continued on next column)

(continued)

*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 11/20/20 (ECHA, 2018).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for ethyl octanoate 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	0.73
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	0.36
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.51
5D	Baby cream, oil, talc	0.12
6	Products with oral and lip exposure	1.2
7	Products applied to the hair with some hand contact	4.0
8	Products with significant ano-genital exposure (tampon)	0.12
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)	7.6
10B	Aerosol air freshener	14
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.12
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 octanoate, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 40%, 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 octanoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of ethyl octanoate 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 octanoate 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, 2016b). 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 octanoate. 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 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, 2016a). 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: None.

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

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for ethyl octanoate 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 octanoate. A subchronic toxicity study was conducted in weanling Osborne-Mendel rats. Groups of 10 rats/sex/dose were fed diets containing test material, ethyl octanoate (ethyl caprylate), at dose levels of 0, 1000, 2500, and 10000 ppm for 17 weeks. No treatment-related changes were reported on growth, hematological parameters, and histopathology at any dose levels. 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 et al., 1967; WHO, 1997).

Read-across material ethyl hexanoate (CAS # 123-66-0; see Section VI) has an OECD 422/GLP combined repeated dose toxicity with a 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 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 (GGT) 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, 2017c; 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. Thus, the NOAEL from the more robust OECD 422 study for a read-across material was selected for this safety assessment.

Therefore, the ethyl octanoate 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 octanoate, 333/0.001, or 333000.

In addition, the total systemic exposure to ethyl octanoate (1.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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 reference dose for ethyl octanoate 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 and Griepentrog, 1967

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

11.1.3. Reproductive toxicity

The MOE for ethyl octanoate 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 octanoate. 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 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 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 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, 2017c; ECHA, 2017a). **Therefore, the ethyl octanoate 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 octanoate, 1000/0.001, or 1000000.**

In addition, the total systemic exposure to ethyl octanoate (1.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5), ethyl octanoate 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 octanoate. Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5; see Section VI), ethyl octanoate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1; 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) (RIFM, 2002a). In 2 separate human maximization tests with limited challenge protocol information, 2/25 subjects exhibited sensitization reactions with 2% (1380 μg/cm^2) ethyl octanoate in petrolatum; however, in an additional test, no skin sensitization reactions were observed with ethyl octanoate when tested at 2% (1380 μg/cm^2) in petrolatum (RIFM, 1975). Additionally, in a confirmatory 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, 2018).

Based on the available data on read-across material methyl octanoate, summarized in Table 1, ethyl octanoate 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: 12/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl octanoate would not be expected to present a concern for phototoxicity or photoallergenicity.

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

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
4900 [1]	Weak	4724	NA	1380	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.

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

[2] Data derived from CNIH or HMT.

[3] WoE NESIL limited to 2 significant figures.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for ethyl octanoate 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 et al., 2009). Based on the lack of absorbance, ethyl octanoate 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 et al., 2009).

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on ethyl octanoate. Based on the Creme RIFM Model, the inhalation exposure is 0.022 mg/day. This exposure is 63.64 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/09/18.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl octanoate 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 octanoate 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 octanoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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 octanoate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation***

RIFM, 2001a: A study was conducted to determine the biodegradability of the test material in a Closed Bottle Test as described in the OECD 301D guideline. Under the conditions of this study, biodegradation of 22% was observed at 28 days.

RIFM, 2002b: The ready biodegradability of the test material was evaluated in a Modified Strum Test according to the OECD 301B method. Biodegradation of 16% was observed after 28 days.

RIFM, 2002c: The biodegradability of the test material was evaluated in a modified CO_2 evolution test (Modified Sturm Test) according to the OECD 301B method. Biodegradation of 91% was observed.

RIFM, 2011: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Biodegradation of 81% was observed after 28 days.

Ecotoxicity

RIFM, 2001b: A *Daphnia magna* immobilization test was conducted according to the OECD 202 part I method under static conditions. The EL50 after 48 h based on nominal test concentrations was reported to be 5.9 mg/L.

RIFM, 2002d: A *Daphnia magna* immobilization test was conducted according to the OECD 202 part I method under static conditions. Under the conditions of this study, the test material EC50 after 48 h based on mean measured concentrations was reported to be 7.9 mg/L.

RIFM, 2017a: 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 mean measured concentrations was reported to be greater than 1.38 mg/L.

RIFM, 2017b: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h ErC50 based on initial measured concentration for growth rate was reported to be 5.57 mg/L, and for EyC50 based on yield was reported to be 2.83 mg/L.

Other available data

Ethyl octanoate has been registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since ethyl octanoate has passed the screening criteria, measured data is included for completeness only.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.47	4.47
Biodegradation Factor Used	1	1

(*continued on next page*)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.65			1000000	0.00165	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.017	3.455	1.104	10000	0.1104	Esters
ECOSAR Acute Endpoints **(Tier 2)**	3.346	2.246	3.339			Neutral Organics

(*continued*)

Exposure	Europe (EU)	North America (NA)
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1104 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: 12/09/20.

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.2021.112500.

Appendix

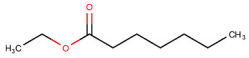
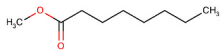
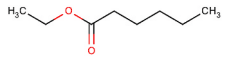
Read-across Justification

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 choice of the alert system.

	Target Material	Read-across	
Principal Name	Ethyl octanoate	Methyl octanoate	Ethyl hexanoate
CAS No.	106-32-1	111-11-5	123-66-0
Structure			
Similarity (Tanimoto Score)		0.88	0.88
Read-across Endpoint		• Skin sensitization	• Genotoxicity • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_9H_{18}O_2$	$C_9H_{18}O_2$	$C_8H_{16}O_2$
Molecular Weight	158.24	158.24	144.21
Melting Point (°C, EPI Suite)	−20.94	−20.94	−32.64
Boiling Point (°C, EPI Suite)	190.83	190.83	170.05
Vapor Pressure (Pa @ 25°C, EPI Suite)	91.5	68.4	240
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.8	3.32	2.83
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	101.9	64.4	629
J_{max} (mg/cm^2/h, SAM)	22.75	5.586	36.394
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	9.6E-004	9.73E+001	7.33E+001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found		No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found		No alert found
Carcinogenicity (ISS)	Non-carcinogen (low reliability)		Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found		No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found		No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found		No alert found
Oncologic Classification	Not classified		Not classified
Repeated Dose			
Repeated Dose (HESS)	Not categorized		Urethane (Renal toxicity) Alert
Reproductive			
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)	
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	
Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	No alert found		
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	(N/A)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on ethyl octanoate (CAS # 106-32-1). Hence, *in silico* evaluation was conducted to determine read-across

analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, methyl octanoate (CAS # 111-11-5) and ethyl hexanoate (CAS # 123-66-0) 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 octanoate (CAS # 106-32-1) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - The key difference between the target material and the read-across analog is that the target is an octanoate 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.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - 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.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Ethyl hexanoate (CAS # 123-66-0) was used as a read-across analog for the target material ethyl octanoate (CAS # 106-32-1) for the genotoxicity, repeated dose, and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - The key difference between the target material and the read-across analog is that the target material is an octanoic 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.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog do not have alerts of toxicity. Data are consistent with the *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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.

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II. Published by the author: Montclair, NJ (USA).

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., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

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

ECHA, 2017b. European chemical agency read-across assessment framework. ECHA read-across assessment framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

ECHA, 2018. Ethyl Octanoate Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/23963/1/2.

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: November 16, 2020. Volume Publish Ahead of Print Issue. https://doi.org/10.1097/DER.0000000000000684.

OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment.* ENV/JM/HA(2015)7. 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.), 2001a. Study on the Ready Biodegradability of Ethyl Octanoate (Ethyl Caprylate). Unpublished Report from Symrise. RIFM Report Number 60271. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. Study on the Acute Toxicity towards Daphnia with Ethyl Octanoate (Ethyl Caprylate). Unpublished Report from Symrise. RIFM Report Number 60274. RIFM, Woodcliff Lake, NJ, USA.

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

RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. Ready Biodegradability - Modified Sturm Test with Ethyl Octanoate (Ethyl Caprylate). Unpublished Report from Symrise. RIFM Report Number 60272. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002c. The Determination of Ready Biodegradability of Ethyl Octanoate (Ethyl Caprylate) in a Modified CO2 - Evolution Test (Modified Sturm Test). Unpublished Report from Symrise. RIFM Report Number 60273. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002d. Ethyl Octanoate (Ethyl Caprylate): Acute Immobolisation Test (48h) to Daphnia Magna STRAUS. Unpublished Report from Symrise. RIFM Report Number 60275. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Ready Biodegradability of Ethyl Octanoate (Ethyl Caprylate). Unpublished Report from Givaudan. RIFM Report Number 62700. RIFM, Woodcliff Lake, NJ, USA.

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

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Ethyl Octanoate (Ethylcaprylat): Salmonella typhimurium and Escherichia coli Reverse Mutation Assay. Unpublished Report from RIFM Report Number 71137. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017a. Ethyl Octanoate (Ethyl Caprylate): Fish (Zebrafish), Acute Toxicity Test, Semi-static, 96 Hours. Unpublished Report from Symrise. RIFM Report Number 72228. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. Ethyl Octanoate (Ethylcaprylat): Alga, Growth Inhibition Test with Pseudokirchneriella Subcapitata, 72 Hours. Unpublished Report from RIFM Report Number 72643. RIFM, Woodcliff Lake, NJ, USA.

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

RIFM (Research Institute for Fragrance Materials, Inc.), 2017d. Exposure Survey 16, May 2017.

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

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 Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.

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

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., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 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, 164–176.

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.

WHO, 1997. WHO Technical Report Series 868. Safety Evaluation of Certain Food Additives and Contaminants. Joint FAO/WHO Expert Committee on Food Additives (JECFA). https://apps.who.int/iris/bitstream/handle/10665/41962/WHO_TRS_868.pdf;jsessionid=93D36EAFADE20F9061A3782A692AD927?sequence=1.