Food and Chemical Toxicology 156 (2021) 112572

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, methyl hexanoate, CAS Registry Number 106-70-7

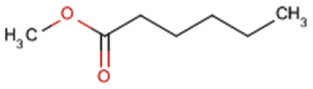
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], 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), 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: 041621. 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: Methyl hexanoate CAS Registry Number: 106-70-7

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.2021.112572
Received 16 April 2021; Received in revised form 24 August 2021; Accepted 13 September 2021
Available online 20 September 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, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

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

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

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

Methyl hexanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog methyl valerate (CAS # 624-24-8) show that methyl hexanoate is not expected to be genotoxic. Data on read-across 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 methyl hexanoate and read-across analog methyl octanoate (CAS # 111-11-5) provided methyl hexanoate a No Expected Sensitization Induction Level (NESIL) of 4700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl hexanoate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog butyl propionate (CAS # 590-01-2). The environmental endpoints were evaluated; methyl hexanoate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

(*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 (2017)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	RIFM (2017)
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: NOAEC = 1331.19 mg/m^3.	Banton (2000)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 3.3 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 16.9 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 88.74 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 88.74 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.08874 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** Methyl hexanoate
2. **CAS Registry Number:** 106-70-7
3. **Synonyms:** Hexanoic acid, methyl ester; Methyl caproate; ｱﾙｶﾝ酸(C = 6 ~ 10)ｱﾙｷﾙ(C = 1 ~ 10); Methyl hexanoate
4. **Molecular Formula:** $C_7H_{14}O_2$
5. **Molecular Weight:** 130.19
6. **RIFM Number:** 1028
7. **Stereochemistry:** No isomeric center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 151 °C (Fragrance Materials Association [FMA] Database), 148.37 °C (EPI Suite)
2. **Flash Point:** 38 °C (Globally Harmonized System), 102 °F; CC (FMA Database)
3. **Log K_{ow}:** 2.34 (EPI Suite)
4. **Melting Point**: 44.6 °C (EPI Suite)
5. **Water Solubility:** 925.9 mg/L (EPI Suite)
6. **Specific Gravity:** 0.885 (FMA Database)
7. **Vapor Pressure:** 2.96 mm Hg at 20 °C (EPI Suite v4.0), 2.7 mm Hg 20 °C (FMA Database), 4.1 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:** Colorless, oily liquid with a powerful, ethereal, and diffusive sweet odor, and sweet-fruity, mild pineapple-apple-apricot taste (Arctander, 1969)

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0033% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.000083 mg/kg/day or 0.0061 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00066 mg/kg/day (RIFM, 2020b)

*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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer classification

Class I, Low

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

6.2. Analogs selected

a. **Genotoxicity:** Methyl valerate (CAS # 624-24-8)
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

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

Acerola (*Malpighia*)
Annatto (*Bixa orellana* L.)
Apple brandy (*Calvados*)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Babaco fruit (*Carica pentagona* Heilborn)
Beef.
Bilberry wine.
Black currants (*Ribes nigrum* L.)
Blackberry brandy.
Blue cheeses.
Cape gooseberry (*Physalis peruviana* L.)
Capers (*Capparis spinoza*)
Capsicum species.
Cashew apple (*Anacardium occidentale*)
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cheddar cheese.
Cheese, various types.
Cherimoya (*Annona cherimolia* Mill.)
Chinese liquor (baijiu)
Chinese quince (*Pseudocydonia sinensis* Schneid)
Cider (Apple wine)
Citrus fruits.
Cloudberry (*Rubus chamaemorus* L.)
Coffee.
Custard apple, atemoya (*Annona atemoya*)
Durian (*Durio zibethinus*)
Gabiroba (*Campomanesia xanthocarpa*)
Grape (*Vitis* species)
Guava and feyoa
Honey.
Hop (*Humulus lupulus*)
Kiwifruit (*Actinidia chinensis,* syn. *A. deliciosa*)
Lamb and mutton.
Lamb's lettuce (*Valerianella locusta*)
Licorice (*Glycyrrhiza* species)
Loganberry juice (*Rubus ursinus* var. *loganobaccus*)
Malt.
Mangifera species.
Matsutake (*Tricholoma matsutake*)
Melon.
Milk and milk products.
Mountain papaya (*C. candamarcensis, C. pubescens)*
Muruci (*Byrsonima crassifolia*)
Mushroom.
Naranjilla fruit (*Solanum quitoense* Lam.)
Nectarine.
Noni (*Morinda citrifolia* L.)
Olive (*Olea europaea*)
Oysters.
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species)
Pawpaw (*Asimina triloba* Dunal.)
Peanut (*Arachis hypogaea* L.)
Pepper (*Piper nigrum* L.)
Pineapple (*Ananas comosus*)
Plum (*Prunus* species)
Potato (*Solanum tuberosum* L.)
Quince, marmelo (*Cydonia oblonga* Mill.)
Raspberry, blackberry, and boysenberry.
Rye bread.
Soursop (*Annona muricata* L.)
Spineless monkey orange (*Strychnos madagasc.*)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)

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

9. REACH dossier

Available; accessed 01/04/21 (ECHA, 2013)

10. Conclusion

The maximum acceptable concentrations[a] in finished products for methyl hexanoate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.36
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	1.1
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	0.27
8	Products with significant ano-genital exposure (tampon)	0.17
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.6
10B	Aerosol air freshener	9.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.17
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For methyl hexanoate, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 4700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, methyl hexanoate does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Methyl hexanoate was assessed in the BlueScreen assay and found positive for cytotoxicity and negative for genotoxicity in the presence and absence of metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenicity of methyl hexanoate. The mutagenic activity of read-across material methyl valerate (CAS # 624-24-8) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with methyl valerate 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 dose in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, methyl valerate was not mutagenic in the Ames test, and this can be applied to methyl hexanoate.

There are no studies assessing the clastogenicity of methyl hexanoate. The clastogenic activity of methyl valerate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with methyl valerate in DMSO at concentrations up to 1160 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Methyl valerate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum dose in either non-activated or S9-activated test systems (RIFM, 2016a). Under the conditions of the study, methyl valerate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be applied to methyl hexanoate.

Based on the available data, methyl hexanoate 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 MOE for methyl hexanoate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on methyl hexanoate. Read-across material, ethyl hexanoate (CAS # 123-66-0; see Section VI), has sufficient repeated dose toxicity data that can be used to support the repeated dose toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered test material ethyl hexanoate (ethyl caproate) at doses of 0, 100, 300, or 1000 mg/kg/day via oral gavage. Males were dosed for at least 50 days (2 weeks prior to mating and continued through the day before euthanasia), while females were dosed for 2 weeks prior to mating and continued through lactation day (LD) 13. Additional animals (6 rats/sex/group) in the control and high-dose recovery groups received ethyl caproate but were not mated; they were assigned to a 2-week period of recovery. One female in the control group was euthanized on LD 3 because all pups were found

expired. This was considered to be incidental since it was observed in the control group, and there were no clinical signs of toxicity. At 1000 mg/kg/day, statistically significant increased prothrombin time in both sexes and statistically significant increased kidney weights in females were observed. Furthermore, statistically significant decreases in gamma glutamyl transpeptidase were observed in all treatment group males. A statistically significant increase in thyroid hormone (T4) was observed in adult males and pups of the highest-dose group. Since there were no correlated microscopic findings associated with any of the alterations observed in the highest-dose group, these findings were not considered to be toxicologically relevant. The NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2017; ECHA, 2017).

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.

Therefore, the methyl hexanoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl hexanoate NOAEL in mg/kg/day by the total systemic exposure to methyl hexanoate, 333/0.00066, or 504545.

In addition, the total systemic exposure to methyl hexanoate (0.66 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.

11.1.2.1.1. 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, 2020c) 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 methyl hexanoate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: Alfin-Slater (1965).

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

11.1.3. Reproductive toxicity

The MOE for methyl hexanoate 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 methyl hexanoate. 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 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 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, 2017; ECHA, 2017).

Therefore, the methyl hexanoate MOE for the reproductive toxicity endpoint can be calculated by dividing the ethyl hexanoate NOAEL in mg/kg/day by the total systemic exposure to methyl hexanoate, 1000/0.00066, or 1515152.

In addition, the total systemic exposure to methyl hexanoate (0.66 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), methyl hexanoate is considered a skin sensitizer with a defined NESIL of 4700 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for methyl hexanoate. Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5; see Section VI), methyl hexanoate 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 a reported EC3 value of 19.6% (4900 μg/cm^2) based on linear regression (RIFM, 2002). In a Buehler delayed contact hypersensitivity test, methyl hexanoate was considered a non-sensitizer (ECHA, 2013). In a human maximization test, no skin sensitization reactions were observed with the target material methyl hexanoate when tested at 4% (2760 μg/cm^2) in petrolatum (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 4724 μg/cm^2 of the 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, methyl hexanoate is considered to be a weak skin sensitizer with a defined NESIL of 4700 μg/cm^2. Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020c) 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 along with existing data, methyl hexanoate would not be expected to present a concern for phototoxicity.

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

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
4900 [1]	Weak	4724	2760	NA	4700

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

[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.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for methyl hexanoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, methyl hexanoate 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 methyl hexanoate; 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 was reported (Banton, 2000; Ulrich, 2000).

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

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

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

The 95th percentile calculated exposure was reported to be 0.0061 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 0.0094 mg/kg lung weight/day resulting in a MOE of 5412234 (i.e., [50,875 mg/kg lung weight/day]/[0.0094 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 0.0061 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: 12/10/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl hexanoate 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, methyl hexanoate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC is < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify methyl hexanoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be

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

11.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl hexanoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Methyl hexanoate has been registered under REACH, and the following data is available (ECHA, 2013):

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 based on mean measured concentration was reported to be 28 mg/L (95% CI: 24–31 mg/L).

An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 based on mean measured concentration was reported to be 11 mg/L and 5.1 mg/L for growth rate and biomass, respectively.

11.2.3. Risk assessment refinement

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

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.34	2.34
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.08874 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/08/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/16/21.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	88.74			1000000	0.08874	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112572.

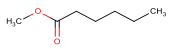
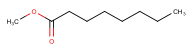
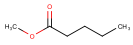
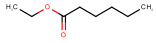
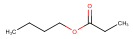
Appendix

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, 2017).

- 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 Material			
Principal Name	Methyl hexanoate	Methyl octanoate	Methyl valerate	Ethyl hexanoate	Butyl propionate
CAS No.	106-70-7	111-11-5	624-24-8	123-66-0	590-01-2
Structure					
Similarity (Tanimoto Score)		0.66	0.78	0.8	0.65
Read-across Endpoint		• Skin sensitization	• Genotoxicity	• Repeated dose toxicity • Reproductive toxicity	• Respiratory toxicity
Molecular Formula	$C_7H_{14}O_2$	$C_9H_{18}O_2$	$C_6H_{12}O_2$	$C_8H_{16}O_2$	$C_7H_{14}O_2$
Molecular Weight	130.19	158.24	116.16	144.21	130.19
Melting Point (°C, EPI Suite)	−44.60	−20.94	−56.83	−32.64	−44.60
Boiling Point (°C, EPI Suite)	148.37	190.83	125.79	170.05	148.37
Vapor Pressure (Pa @ 25°C, EPI Suite)	547	68.4	1.5E+003	240	620
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	2.34	3.32	1.96	2.83	2.34
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1330	64.4	5060	629	925.9
J_{max} (mg/cm^2/h, SAM)	59.385	5.586	235.510	36.394	59.9
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	5.52E+001	9.73E+001	4.16E+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)	• 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		• No alert found • No alert found		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material			
***In Vivo* Mutagenicity (Micronucleus, ISS)**					
Oncologic Classification	• Not classified		• Not classified		
Repeated Dose Toxicity					
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)			
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found			
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found			
Local Respiratory Toxicity					
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• No alert found				• No alert found
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on methyl hexanoate (CAS # 106-70-7). 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), methyl valerate (CAS # 624-24-8), 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 methyl hexanoate (CAS # 106-70-7) 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 hexanoate 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 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.
- Methyl valerate (CAS # 624-24-8) was used as a read-across analog for the target material methyl hexanoate (CAS # 106-70-7) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target material is a hexanoate ester, whereas the read-across analog is a valerate ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog do not have alerts of toxicity. Data are consistent with *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.

- Ethyl hexanoate (CAS # 123-66-0) was used as a read-across analog for the target material methyl hexanoate (CAS # 106-70-7) for the 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 a methyl ester, whereas the read-across analog is an ethyl 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 *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.
- Butyl propionate (CAS # 590-01-2) was used as a read-across analog for the target material methyl hexanoate (CAS # 106-70-7) for the local respiratory 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 a hexanoate ester, while the read-across analog is a propionate ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - 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 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.
  - 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

Alfin-Slater, R.B., Morris, R.S., Hansen, H., Proctor, J.F., 1965. Effects of non-essential fatty acids on essential fatty-acid deficiency. J. Nutr. 87 (2), 168–171.

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), I and II. Published by the author, Montclair, NJ (USA).

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.

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, 2013. Methyl hexanoate registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/5296/1.

ECHA, 2017. European Chemical Agency Read-Across Assessment Framework. ECHA. Read-across Assessment Framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

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. 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.), 1977. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1691.

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.), 2013. Report on the Testing of Methyl Hexanoate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66184.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Methyl Valerate: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69824.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Methyl Valerate: Bacterial Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69825.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. 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.), 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, Woodcliff Lake, NJ, USA. RIFM report number 76272.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Exposure Survey, 28. August 2020.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020c. 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., 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.
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.