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RIFM fragrance ingredient safety assessment, methyl decanoate, CAS Registry Number 110-42-9

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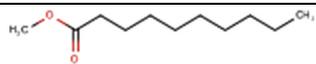
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Name: Methyl decanoate CAS Registry Number: 110-42-9



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

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

DRF - Dose Range Finding

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 Observed Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

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,

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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 decanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl decanoate is not genotoxic. Data on read-across analog ethyl hexanoate (CAS # 123-66-0) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data on read-across analog methyl octanoate (CAS # 111-11-5) provided methyl decanoate a No Expected Sensitization Induction Level (NESIL) of 4700 $\mu\text{g}/\text{cm}^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl decanoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to methyl decanoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; methyl decanoate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1 .

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2016b; RIFM, 2016a)

Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day. RIFM (2017)

Reproductive Toxicity: RIFM (2017)

Developmental toxicity and Fertility NOAEL: 1000 mg/kg/day.

Skin Sensitization: NESIL = 4700 $\mu\text{g}/\text{cm}^2$. RIFM (2018)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.2 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Critical Measured Value: (EPI Suite v4.11; US EPA, 2012a)

Screening-level: 15.9 L/kg

Ecotoxicity: Critical Ecotoxicity Endpoint: (RIFM Framework; Salvitto, 2002)
Fish LC50: 2.507 mg/L

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvitto, 2002)

Critical Ecotoxicity Endpoint: (RIFM Framework; Salvitto, 2002)
Fish LC50: 2.507 mg/L

RIFM PNEC is: 0.002507 $\mu\text{g}/\text{L}$

• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe (No VoU): Not applicable; cleared at the screening-level

1. Identification

- Chemical Name:** Methyl decanoate
- CAS Registry Number:** 110-42-9
- Synonyms:** Decanoic acid, methyl ester; Methyl caprate; Methyl decanoate
- Molecular Formula:** $\text{C}_{11}\text{H}_{22}\text{O}_2$
- Molecular Weight:** 186.29
- RIFM Number:** 6692

7. **Stereochemistry:** No stereocenter present, and therefore no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 229.67 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{ow}:** 4.3 (EPI Suite)
4. **Melting Point:** 1.67 °C (EPI Suite)
5. **Water Solubility:** 8.787 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0699 mm Hg at 20 °C (EPI Suite v4.0), 0.107 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
9. **Appearance/Organoleptic:** Colorless oily liquid. Oily, winey, slightly fruity odor when pure. Winey-honey-like taste, quite powerful (Arctander, 1969)

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. **95th Percentile Concentration in Fine Fragrance:** 0.0001 % (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.0000039 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00027 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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

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

6.2. Analogs Selected

- a. **Genotoxicity:** None
- 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

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

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

Apple brandy (<i>Calvados</i>)	Cape gooseberry (<i>Physalis peruviana</i> L.)
Apple fresh (<i>Malus</i> species)	Capsicum species
Banana (<i>Musa sapientum</i> L.)	Cheddar cheese
Beer	Cheese, various types
Black currants (<i>Ribes nigrum</i> L.)	Cherimoya (<i>Annona cherimolia</i> Mill.)
Blue cheeses	Citrus fruits
Brassica Campestris	Coconut (<i>Cocos nucifera</i> L.)
Elderberry (<i>Sambucus nigra</i> L.)	Pear brandy
Grape (<i>Vitis</i> species)	Pineapple (<i>Ananas comosus</i>)
Grape brandy	Plum (<i>Prunus</i> species)
Hop (<i>Humulus lupulus</i>)	Plum brandy
Litchi wine	Prickly pear (<i>Opuntia ficus indica</i>)
Milk and milk products	Raspberry, blackberry, and boysenberry
Mountain papaya (<i>C. Candamarcensis</i> , <i>C. pubescens</i>)	Rhubarb
Mushroom	Rum
Nectarine	Spineless monkey orange (<i>Strychnos madagasc.</i>)
Noni (<i>Morinda citrifolia</i> L.)	Starfruit (<i>Averrhoa carambola</i> L.)
Olive (<i>Olea europaea</i>)	Strawberry (<i>Fragaria</i> species)
Papaya (<i>Carica papaya</i> L.)	Swiss cheeses
Pawpaw (<i>Asimina triloba</i> Dunal.)	Tequila (<i>Agave tequilana</i>)
Pear (<i>Pyrus communis</i> L.)	Vanilla

*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, 2011).

10. Conclusion

The maximum acceptable concentrations^a in finished products for methyl decanoate are detailed below.

IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%) ^c
1	Products applied to the lips (lipstick)	0.36
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	2.2
4	Products related to fine fragrances	2.0
5 A		0.51

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IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%) ^c
	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	
5 B	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	4.1
8	Products with significant anogenital exposure (tampon)	0.17
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.9
10 A	Household care products with mostly hand contact (hand dishwashing detergent)	9.9
10 B	Aerosol air freshener	9.9
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: ^aMaximum 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 decanoate, 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/cm².

^bFor 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>).

^cCalculations by Creme RIFM Aggregate Exposure Model v3.1.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, methyl decanoate does not present a concern for genotoxicity.

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

The mutagenic activity of methyl decanoate 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 decanoate 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 decanoate was not mutagenic in the Ames test.

The clastogenic activity of methyl decanoate 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 decanoate in DMSO at concentrations up to 225 µg/mL in the presence and absence of S9 for 3 and 24 h. Methyl decanoate 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 decanoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Therefore, the methyl decanoate 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 decanoate 333/0.00027, or 1,233,333.

In addition, the total systemic exposure to methyl decanoate (0.27 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 reference dose for methyl decanoate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, $100 = 3.33 \text{ mg/kg/day}$.

*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 decanoate 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 decanoate. 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 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; also available in ECHA, 2017a). **Therefore, the methyl decanoate 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 decanoate, $1000/0.00027$, or 370,370.**

In addition, the total systemic exposure to methyl decanoate (0.27 $\mu\text{g/kg/day}$) is below the TTC (30 $\mu\text{g/kg/day}$; 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 decanoate is considered a skin sensitizer with a defined NESIL of 4700 $\mu\text{g/cm}^2$.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are

Table 1

Data Summary for ethyl hexanoate as read-across material for methyl decanoate.

LLNA Weighted Mean EC3 Value $\mu\text{g/cm}^2$ (No. Studies)	Potency Classification Based on Animal Data ^a	Human Data			
		NOEL-CNIH (Induction) $\mu\text{g/cm}^2$	NOEL-HMT (Induction) $\mu\text{g/cm}^2$	LOEL ^b (Induction) $\mu\text{g/cm}^2$	WoE NESIL ^c $\mu\text{g/cm}^2$
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.

available for methyl decanoate. Based on the existing data and read-across material methyl octanoate (CAS # 111-11-5; see Section VI), methyl decanoate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; ToxTree v3.1.0; OECD Toolbox v4.2). In a local lymph node assay (LLNA), read-across material methyl octanoate was found to be sensitizing with an EC3 value of 19.6 % (4900 $\mu\text{g/cm}^2$) based on linear regression (RIFM, 2002). In a confirmation of no induction in humans test (CNIH) with 4724 $\mu\text{g/cm}^2$ 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, methyl decanoate is considered to be a weak skin sensitizer with a defined NESIL of 4700 $\mu\text{g/cm}^2$. 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, methyl decanoate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for methyl decanoate 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 decanoate 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 $\text{L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry, 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 methyl decanoate 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 decanoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0000039 mg/day. This exposure is 358,974 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; [Carthew, 2009](#)); therefore, the exposure at the current level of use is deemed safe.

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 decanoate 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.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>2.507</u>			1000000	0.002507	

Following the RIFM Environmental Framework, methyl decanoate 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 decanoate 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 decanoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation:** No data available.

Ecotoxicity: No data available.

Other available data: Methyl decanoate has been registered under REACH, and the following data is available ([ECHA, 2011](#)):

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48 h EC50 value based on the mean measured concentration was reported to be 1.1 mg/L (95 % CI: 0.94–1.4 mg/L).

An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 value based on the mean measured concentration was reported to be greater than 0.055 mg/L for growth rate and biomass.

11.2.3. Risk assessment refinement

Since methyl decanoate 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 $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.3	4.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	<1
Risk Characterization: PEC/PNEC	N/A	< 1

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

The RIFM PNEC is 0.002507 $\mu\text{g/L}$. The revised PEC/PNECs for EU (No VoU) and NA are not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/10/20.

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://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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.2021.112462>.

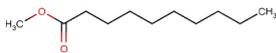
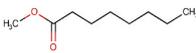
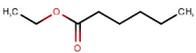
Appendix

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 alert system.

	Target Material	Read-across Material	
Principal Name	Methyl decanoate	Methyl octanoate	Ethyl hexanoate
CAS No.	110-42-9	111-11-5	123-66-0
Structure			
Similarity (Tanimoto Score)		0.88	0.8
Read-across Endpoint		• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	C ₁₁ H ₂₂ O ₂	C ₉ H ₁₈ O ₂	C ₈ H ₁₆ O ₂

(continued on next page)

(continued)

Principal Name	Target Material	Read-across Material	
	Methyl decanoate	Methyl octanoate	Ethyl hexanoate
Molecular Weight	186.3	158.24	144.21
Melting Point (°C, EPI Suite)	1.67	-20.94	-32.64
Boiling Point (°C, EPI Suite)	229.67	190.83	170.05
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.107	68.4	240
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.3	3.32	2.83
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	8.8	64.4	629
J_{max} (mg/cm²/h, SAM)	1.2	5.586	36.394
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	1.7E-003	9.73 E+001	7.33 E+001
Repeated Dose (HESS)	Not categorized		Urethane (Renal toxicity) Alert
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure Toxicant (good reliability)
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		
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 Sensitization (OECD QSAR Toolbox v4.2)	No alert found		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	Supplemental Data 1	Supplemental Data 2	Supplemental Data 3

Summary

There are insufficient toxicity data on methyl decanoate (CAS # 110-42-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties, and expert judgment, methyl octanoate (CAS # 111-11-5) 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 methyl decanoate (CAS # 110-42-9) for the skin sensitization endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
 - o The key difference between the target material and the read-across analog is that the target is an octanoate ester, whereas the read-across analog is a decanoate 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.
- Ethyl hexanoate (CAS # 123-66-0) was used as a read-across analog for the target material methyl decanoate (CAS # 110-42-9) for the repeated dose and reproductive toxicity endpoints.
 - o The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
 - o The key difference between the target material and the read-across analog is that the target material is a decanoate ester, whereas the read-across analog is a hexanoate ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
 - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - o The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable 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 the *in silico* alerts.
 - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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