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Short Review

RIFM fragrance ingredient safety assessment, methyl 2-nonenoate, CAS Registry Number 111-79-5

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Genotoxicity
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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. Methyl 2-nonenoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) show that methyl 2-nonenoate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to methyl 2-nonenoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from the target and read-across analog isobutyl-2-butenoate (CAS # 589-66-2) do not indicate the material is a sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; methyl 2-nonenoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl 2-nonenoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

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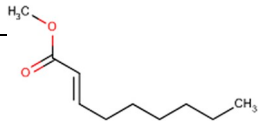
Name: Methyl 2-nonenoate
CAS Registry Number: 111-79-5



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
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., 2015, 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
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
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

Methyl 2-nonenoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) show that methyl 2-nonenoate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to methyl 2-nonenoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from the target and read-across analog isobutyl-2-butenoate (CAS # 589-66-2) do not indicate the material is a sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; methyl 2-nonenoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl 2-nonenoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2017a; RIFM, 2016)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Data do not indicate sensitization. RIFM (2013)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.
(UV Spectra, RIFM DB; RIFM, 1981a; RIFM, 1981b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 69% (OECD 302C) RIFM (2004)
Bioaccumulation: Screening-level: 109 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 1.542 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 1.542 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1542 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

1. Identification

1. **Chemical Name:** Methyl 2-nonenoate
2. **CAS Registry Number:** 111-79-5
3. **Synonyms:** Methyl nonylenate; Neofolione; 2-Nonenoic acid, methyl ester; 脂肪酸(C = 9 ~ 24)ｱﾙｷﾙ(C = 1 ~ 10)ｴｽﾃﾙ; Methyl non-2-enoate; Methyl 2-nonenoate
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight:** 170.25
6. **RIFM Number:** 682
7. **Stereochemistry:** Isomer not specified. One geometric center and 2 total geometric isomers possible.

2. Physical data

1. **Boiling Point:** 216.64 °C (EPI Suite)
2. **Flash Point:** 91 °C (GHS), 195 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.4 at 35 °C (RIFM, 2002a), 3.6 (EPI Suite)
4. **Melting Point**: 10.31 °C (EPI Suite)
5. **Water Solubility:** 52.1 mg/L (EPI Suite)
6. **Specific Gravity:** 0.895 (FMA Database)
7. **Vapor Pressure:** 0.103 mm Hg @ 20 °C (EPI Suite v4.0), 0.05 mm Hg @ 20 °C (FMA Database), 0.156 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 $L\,mol^{-1}\cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to slightly yellow liquid with strong, violet-leaf odor; fatty green odor reminiscent of violet leaf and coconut at the same time *(Arctander, 1969)

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.013% (RIFM, 2018)
3. **Inhalation Exposure*:** 0.000092 mg/kg/day or 0.0068 mg/day (RIFM, 2018)
4. **Total Systemic Exposure**:** 0.00067 mg/kg/day (RIFM, 2018)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015, 2017; Safford et al., 2015; Safford et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Isobutyl 2-butenoate (CAS # 589-66-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

Methyl 2-nonenoate is not reported to occur in foods by VCF*:

*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.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 04/19/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, methyl 2-nonenoate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of methyl 2-nonenoate; however, read-across can be made to ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7; see Section 5). The mutagenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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 ethyl *trans*-2,*cis*-4-decadienoate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at

any tested concentration in the presence or absence of S9 (RIFM, 2017a). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl *trans*-2,*cis*-4-decadienoate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with ethyl *trans*-2,*cis*-4-decadienoate in DMSO at concentrations up to 1960 μg/mL in a dose range finding (DRF) study. Micronuclei analysis in the main study was conducted up to 500 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Ethyl *trans*-2,*cis*-4-decadienoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl *trans*-2,*cis*-4-decadienoate does not present a concern for genotoxic potential, and this can be extended to methyl 2-nonenoate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/11/2018.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on methyl 2-nonenoate or on any read-across materials. The total systemic exposure to methyl 2-nonenoate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl 2-nonenoate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to methyl 2-nonenoate (0.67 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/18.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on methyl 2-nonenoate or on any read-across materials. The total systemic exposure to methyl 2-nonenoate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl 2-nonenoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl 2-nonenoate (0.67 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/18.

10.1.4. Skin sensitization

Based on the existing data and read-across material isobutyl 2-butenoate (CAS # 589-66-2), methyl 2-nonenoate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for methyl 2-nonenoate. Existing data and read-across material isobutyl 2-butenoate (CAS # 589-66-2; see Section 5), do not indicate methyl 2-nonenoate is a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v4.1). In a guinea pig maximization test (GPMT), methyl 2-nonenoate did not present reactions indicative of sensitization at 10% (RIFM, 1978). In an open epicutaneous test (OET), methyl 2-nonenoate did not present reactions indicative of sensitization at 100% (RIFM, 1981c). In a human maximization test (HMT), no skin sensitization reactions were observed with methyl 2-nonenoate at 20% (13800 μg/cm^2) (RIFM, 1975). Additionally, in confirmatory human repeat insult patch tests (HRIPT) with 2093 μg/cm^2 and 1937 μg/cm^{2}of read-across material isobutyl 2-butenoate, no reactions indicative of sensitization were observed in any of the 105 and 38 volunteers, respectively (RIFM, 2013; IFF, 1971).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material isobutyl 2-butenoate, methyl 2-nonenoate does not present a concern for skin sensitization.

Additional References: RIFM, 1981d.

Literature Search and Risk Assessment Completed On: 05/29/2018.

10.1.5. Phototoxicity/photoallergenicity

Based on the UV absorption spectra and *in vivo* study data, methyl 2-nonenoate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV absorption spectra indicate no significant absorption between 290 and 500 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In phototoxicity and photoallergenicity studies conducted in guinea pigs, 3% and 10% methyl 2-nonenoate, respectively, were not found to be phototoxic or photoallergenic (RIFM, 1981a; RIFM, 1981b). Based on lack of absorbance and the *in vivo* study data, methyl 2-nonenoate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no significant absorbance in the range of 290–500 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for methyl 2-nonenoate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on methyl 2-nonenoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0068 mg/day. This exposure is 206 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/23/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl 2-nonenoate was performed following the RIFM Environmental Framework (Salvito et al., 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 2-nonenoate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify methyl 2-nonenoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl 2-nonenoate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2004: The inherent biodegradability of the test material was determined by the manometric respirometry test conducted according to the OECD 302C method. Closed flasks containing inoculated mineral medium and 30 mg/L of methyl 2-nonenoate were incubated for 42 days. The biodegradation rate was 69.1% and 68.8% at day 28 and 42, respectively.

RIFM, 2002b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Closed flasks containing inoculated mineral medium and 100 mg/L of methyl 2-nonenoate were incubated for 48 days. The biodegradation rate was 46%, 51%, and 53% at day 10, 28, and 48, respectively.

10.2.2.2. Ecotoxicity. RIFM, 2017b: An algae growth inhibition study was conducted according to the OECD 201 guidelines. Based on mean measured concentration, the 72-h EC50 was reported to be 0.21 mg/L for growth rate and 0.19 mg/L for yield.

RIFM, 2017c: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions in a closed system. The 48-h EC50 based on mean measured concentration was reported to be 2.4 mg/L.

10.2.2.3. Other available data. Methyl 2-nonenoate has been registered under REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Since methyl 2-nonenoate 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>1.872</u>			1,000,000	0.001872	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.662	4.665	<u>1.542</u>	10,000	0.1542	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.152	3.394	4.649			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.4	4.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.1542 µg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 4/26/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110622.

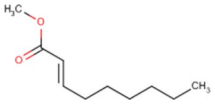
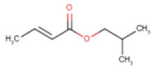
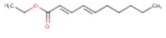
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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 substance 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	
Principal Name	Methyl 2-nonenoate	Isobutyl 2-butenoate	Ethyl *trans*-2,*cis*-4-decadienoate
CAS No.	111-79-5	589-66-2	3025-30-7
Structure			
Similarity (Tanimoto Score)		0.59	0.73
Read-across Endpoint		• Skin sensitization	• Genotoxicity
Formula	$C_{10}H_{18}O_2$	$C_8H_{14}O_2$	$C_{12}H_{20}O_2$
Molecular Weight	170.25	142.20	196.29
Melting Point (°C, EPI Suite)	−10.31	−44.52	10.62

Boiling Point (°C, EPI Suite)	216.64	163.76	258.41
Vapor Pressure (Pa @ 25°C, EPI Suite)	20.8	280	2.31
Log Kow (KOWWIN v1.68 in EPI Suite)	3.60	2.54	4.36
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	52.1	555.2	8.588
Jmax (μg/cm^2/h, SAM)	25.384	193.182	3.248
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	6.05E + 001	3.44E + 001	7.64E + 001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found		• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition-Polarized Alkenes • Alpha, beta-unsaturated esters		• Michael addition-Polarized • Alkenes Alpha, beta- unsaturated esters
Carcinogenicity (ISS)	• NON-Carcinogen (low reliability)		• NON-Carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found		• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found		• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found		• No alert found
Oncologic Classification	• Acrylate reactive functional groups		• Acrylate reactive functional groups
Skin Sensitization			
Protein Binding (OASIS v1.1)	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double b	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double b	
Protein Binding (OECD)	• Michael addition -Polarized alkene - esters	• Michael addition -Polarized alkene - esters	
Protein Binding Potency	• Moderately reactive (GSH)	• Moderately reactive (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double bond	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double bond	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Michael acceptor alert	• Michael acceptor alert	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on methyl 2-nonenoate (CAS # 111-79-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, isobutyl 2-butenoate (CAS # 589-66-2) and ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) were identified as read-across materials with sufficient data for toxicological evaluation.

12. Conclusions

- Isobutyl 2-butenoate (CAS # 589-66-2) was used as a read-across analog for the target material methyl 2-nonenoate (CAS # 111-79-5) for the skin senzitization endpoint.
  - The target substance and the read-across analog are structurally similar and are alpha,beta-unsaturated aliphatic esters.
  - The key difference between the target substance and the read-across analog is that the read-across analog is an isobutyl ester of butenoic acid, whereas the target substance is a methyl ester of nonenoic acid. These structural differences are toxicologically insignificant.
  - Similarity between the target substance 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 substance 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 substance and the read-across analog.
  - The target substance and the read-across analog have protein binding alerts via Michael addition and reactivity towards GSH. Both of these alerts are due to the presence of polarized carbonyl. The data described in the skin sensitization section confirms that the read-across analog does not pose a concern for skin sensitization. Therefore, the predictions are superseded by data.
  - The target substance 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 *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) was used as a read-across analog for the target material methyl 2-nonenoate (CAS # 111-79-5) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and are alpha,beta-unsaturated aliphatic esters.
  - The key difference between the target substance and the read-across analog is that the read-across analog has a conjugated diene alpha to the carbonyl group, whereas the target has a single double bond conjugated to the carbonyl in the same position. This structural difference is toxicologically insignificant.
  - Similarity between the target substance 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 substance 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 substance and the read-across analog.
- ○ The target substance and the read-across analog are Michael acceptors due to the presence of polarized carbonyl groups. The data described in the genotoxicity section show that the read-across analog poses no concern for genetic toxicity. Therefore, based on the structural similarity between the read-across analog and the target substance, and the data for the read-across analog, the alert is superseded by data.
- ○ The target substance 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.

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