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Short Review

RIFM fragrance ingredient safety assessment, methyl 2-nonynoate, CAS Registry Number 111-80-8

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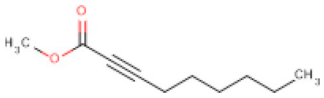

Abbreviation/Definition List:

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

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

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

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

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

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

Methyl 2-nonynoate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl 2-nonynoate is not genotoxic. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class III material, and the exposure is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data provided methyl 2-nonynoate a NESIL of 24 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; methyl 2-nonynoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl 2-nonynoate 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 genotoxic. (Wild et al., 1983)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 24 μg/cm^2. (RIFM, 1989c; RIFM, 1990b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1988b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 99% (OECD 302C) RIFM (1999)
Bioaccumulation: Screening-level: 51.21 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 3.41 mg/L (EPI Suite v4.11; US EPA, 2012a)
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: 3.41 mg/L (EPI Suite v4.11; US EPA, 2012a)
RIFM PNEC is: 0.341 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe < 1

1. Identification

1. **Chemical Name:** Methyl 2-nonynoate
2. **CAS Registry Number:** 111-80-8
3. **Synonyms:** Methyl octine carbonate; Methyl octyne carbonate; MOC; 2-Nonynoic acid, methyl ester; アルキン（C = 7 ~ 8）カルボン酸メチル; 1-ｵｸﾃﾝ-1-ｶﾙﾎﾞﾝ酸ﾒﾁﾙ; Methyl non-2-ynoate; Methyl 2-nonynoate
4. **Molecular Formula:** $C_{10}H_{16}O_2$
5. **Molecular Weight:** 168.23
6. **RIFM Number:** 437

2. Physical data

1. **Boiling Point:** 85 °C @ 3 mm Hg (FMA), 224.53 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA)
3. **Log K_{OW}:** Log Pow = 4.0 (RIFM, 1998b), 3.1 (EPI Suite)
4. **Melting Point**: 37.54 °C (EPI Suite)
5. **Water Solubility:** 142.5 mg/L (EPI Suite)
6. **Specific Gravity:** 0.914 (FMA)
7. **Vapor Pressure:** 0.0443 mm Hg @ 20 °C (EPI Suite v4.0), 0.04 mm Hg 20 °C (FMA), 0.0749 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorption between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Givaudan IFRA (2015) colorless oily liquid, green, violet leaf-like and mimosa like odor more delicate and less acrid than the methyl heptin carbonate (Arctander, Volume II, 1969)

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.006*% (RIFM, 2015)
2. **Inhalation Exposure*:** 0.00003 mg/kg/day or 0.0020 mg/day (RIFM, 2015)
3. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2015)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. Cramer Classification: Class III, High

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

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 (discrete chemical) or composition (NCS)

Methyl 2-nonynoate is not reported to occur in food by the 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.

9. Reach dossier

Available; accessed 06/03/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for methyl 2-nonynoate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.0018
2	Products applied to the axillae	0.00055
3	Products applied to the face/body using fingertips	0.011
4	Products related to fine fragrances	0.010
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.0026
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0026
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.0026
5D	Baby cream, oil, talc	0.0026
6	Products with oral and lip exposure	0.0061
7	Products applied to the hair with some hand contact	0.021
8	Products with significant ano-genital exposure (tampon)	0.0011
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.020
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.072
10B	Aerosol air freshener	0.072

11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.040
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 2-nonynoate, the basis was a predicted skin absorption value of 80% and a skin sensitization NESIL of 24 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (http://www.rifm.org/doc).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, methyl 2-nonynoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Methyl 2-nonynoate was assessed in an Ames assay conducted in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with methyl 2-nonynoate in DMSO (dimethyl sulfoxide) at concentrations up to 3.6 mg/plate in the presence and absence of exogenous metabolically active microsomal mix (S9 mix). No increase in the number of revertant colonies was observed in the tester strains at any concentration (Wild et al., 1983). Under the conditions of the study, methyl 2-nonynoate was considered not mutagenic in the Ames test.

The clastogenic potential of methyl 2-nonynoate was assessed in an *in vivo* micronucleus test in which groups of male and female NMRI mice were administered a single intraperitoneal injection at 3 dose levels up to a maximum of 308 mg/kg of methyl 2-nonynoate in olive oil. Compared to the olive oil-treated controls, no significant increase in the number of micronucleated polychromatic erythrocytes was observed at doses of 154, 231, and 308 mg/kg (Wild et al., 1983). Under the conditions of the study, methyl 2-nonynoate was considered non-clastogenic.

Based on the available data, methyl 2-nonynoate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/01/16.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on methyl-2-nonynoate or any of the read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to methyl-2-nonynoate (0.14 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/25/18.

11.1.3. Developmental and reproductive toxicity

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

11.1.3.1. Risk assessment. There are insufficient developmental and reproductive toxicity data on methyl-2-nonynoate or on any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to methyl-2-nonynoate (0.14 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/25/18.

11.1.4. Skin sensitization

Based on the existing data, methyl 2-nonynoate is considered a moderate skin sensitizer with a defined NESIL of 24 μg/cm^2.

11.1.4.1. Risk assessment. The chemical structure of methyl 2-nonynoate indicates that it is expected to react with skin proteins directly via the Michael addition mechanism (Roberts et al., 2007; Toxtree 2.6.6; OECD Toolbox v3.3). Methyl 2-nonynoate was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, human cell line activation test (h-CLAT), and U-Sens test (Urbisch et al., 2015). However, in a murine local lymph node assay (LLNA), methyl 2-nonynoate was found to be sensitizing with an EC3 value of 2.5% (625 μg/cm^2) (Ryan et al., 2000; Aptula et al., 2007). Additionally, in a human repeat insult patch test (HRIPT) with 118 μg/cm^2 of methyl 2-nonynoate in 3:1 ethanol:diethyl phthalate, reactions indicative of sensitization were observed in 6/138 volunteers (RIFM,

Table 1
Data summary for methyl 2-nonynoate.

LLNA Weighted Mean EC3 Value μg/cm[b] [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
< 1250 estimated 625 [1]	Moderate	24	NA	118	24

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.
[c] WoE NESIL limited to 3 significant figures.

1989a; RIFM, 1990a; RIFM, 1989b). Additionally, in a confirmatory HRIPT with 24 μg/cm^2 of methyl 2-nonynoate in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 100 volunteers (RIFM, 1989c; RIFM, 1990b).

Based on weight of evidence from structural analysis and animal and human studies, methyl 2-nonynoate is a moderate sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 24 μg/cm^2 (Table 1). 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf).

Additional References: McKim et al., 2010; RIFM, 1980a; RIFM, 1980b; RIFM, 1969; RIFM, 1988a; RIFM, 1983; RIFM, 2006; Klecak (1985); Griepentrog (1959); RIFM, 1985a; RIFM, 1988c; RIFM, 1985b; RIFM, 1980c; Klecak et al., 1977; Klecak (1979); RIFM, 1985c; RIFM, 1985d; RIFM, 1986; RIFM, 1964; RIFM, 1980d; RIFM, 1980e.

Literature Search and Risk Assessment Completed On: 08/31/15.

11.1.5. Phototoxicity/photoallergenicity

Based on UV spectra and the available *in vivo* data, methyl 2-nonynoate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV absorption spectra indicate no 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 a guinea pig phototoxicity/photoallergenicity study, application of a solution of 0.08% methyl 2-nonynoate resulted in no observations of phototoxicity after the first induction application, and a single observation of weak, “hardly visible” erythema 24 h after challenge in 1/10 animals. Upon macroscopic and histological examination, the authors characterized it as a “phototoxic-type reaction” and did not consider the animal positive for photoallergenicity (RIFM, 1988b). Based on the lack of absorbance in the critical range, and the available *in vivo* data, methyl 2-nonynoate is not likely to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no 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: 06/20/16.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on methyl 2-nonynoate. Based on the Creme RIFM Model, inhalation exposure is 0.002 mg/day. This exposure is 235 times lower than the Cramer Class III TTC value of 0.47 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: 03/28/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl 2-nonynoate 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-nonynoate 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-nonynoate as either being possibly persistent nor 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 biodegradation, fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on current VoU (2015), methyl 2-nonynoate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 1999: The inherent biodegradability of the test material was evaluated by the manometric respirometry test using fresh activated sludge according to the OECD 302C method. Biodegradation of 99% was observed after 28 days.

RIFM, 1998a: The ready biodegradability of the test material was evaluated by the manometric respirometry test following the OECD 301F method. Under the conditions of this study, biodegradation of 58% was observed after 34 days.

RIFM, 2013: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Biodegradation of 71% was observed after 28 days.

11.2.2.2. Ecotoxicity. RIFM, 2016: An algae growth inhibition test was

conducted according to the OECD 201 method. Based on the mean measured concentration, the 0–72 h EC10 was reported to be 0.29 mg/L for growth and 0.15 mg/L for yield; the EC50 was 0.83 mg/L for growth and 0.36 mg/L for yield; the NOEC was 0.065 mg/L for growth and yield.

11.2.2.3. Other available data. Methyl 2-nonynoate has been registered under REACH and the following additional data is available:

Daphnia magna immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 1.1 mg/L (ECHA, 2017).

11.2.3. Risk assessment refinement

Since methyl-2-nonynoate 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)**	4.129			1000000	0.004129	
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	5.153	9.532	3.410 L	10000	0.341	Esters
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	14.34	9.013	10.20			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.341 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: 04/02/19.

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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 06/03/19.

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.

References

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

Aptula, N., Roberts, D.W., Schultz, T.W., Pease, C., 2007. Reactivity assays for non-animal based prediction of skin sensitisation potential. Toxicology 231 (2–3), 117–118.
Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II Published by the author: Montclair, NJ (USA).
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.
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, 2017. Methyl 2-nonynoate Registration Dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/18707.
Griepentrog, F., 1959. Allergiestudien mit einfachen chemischen substanzen [Allergy studies with simple chemical substances]. Allerg. Asthma 5 (4/5), 224–226.
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.
Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. International Federation Societies Cosmetic Chemists 9/18/79.
Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 152–171.
Klecak, G., Geleick, H., Frey, J.R., 1977. Screening of fragrance materials for allergenicity in the Guinea pig. I. Comparison of four testing methods. Journal of the Society of Cosmetic Chemists Japan 28, 53–64.
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.
McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-medicated gene expression in human skin cells. Cutan. Ocul. Toxicol. 29 (3), 171–192.
RIFM (Research Institute for Fragrance Materials, Inc), 1964. Human Repeated Patch Test on Methyl-2-Nonynoate and Isoeugenol. Unpublished report from International Flavors and Fragrances. RIFM report number 1808. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1969. Skin Sensitization with Methyl 2-nonynoate (Methyl Octine Carbonate) in guinea Pigs. Unpublished report from Givaudan. RIFM report number 56041. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Evaluation of Potential Hazards by Dermal Contact of Fragrance Materials in Human Subjects. Unpublished report from International Flavors and Fragrances. RIFM report number 1982. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Delayed Contact Hypersensitivity Study of Methyl 2-nonynoate in guinea Pigs. Unpublished Report from International Flavors and Fragrances. RIFM report number 2001. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Evaluation of Potential Hazards by Dermal Contact with Fragrance Materials. Unpublished report from International Flavors and Fragrances. RIFM report number 53104. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Skin Irritation and Capacity of Allergenic Sensitization of Methyl 2-nonynoate (Methyl Octine Carbonate) Determined by the Open Epicutaneous Test on guinea Pigs. Unpublished report from Givaudan. RIFM report number 56042. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Skin Irritation and Capacity of Allergenic Sensitization of Methyl 2-nonynoate (Methyl Octine Carbonate) Determined by the Open Epicutaneous Test on guinea Pigs. Unpublished report from Givaudan. RIFM report number 56043. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1983. Guinea Pig Skin Sensitization Test with Methyl 2-nonynoate. Unpublished report from Quest International. RIFM report number 46529. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1985. Closed Epicutaneous Test of Methyl-2-Octynoate, Methyl-2-Nonynoate, Benzyl Acetate, Trans,trans-2,4-Hexadienal, 2-hexylidene Cyclopentanone, Hexen-2-Al, Trans-2-hexenal Diethyl Acetal and Isoeugenol in guinea Pigs. Report to RIFM. RIFM report number 4474. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1985. Guinea Pig Maximization Test. Report to RIFM. RIFM Report Number 4899. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1985. Closed Epicutaneous Test of 2-hexylidenecyclopentanone, Methyl 2-nonynoate and Methyl 2-octynoate in guinea Pigs. Report to RIFM. RIFM report number 5175. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1985. Open and Closed Epicutaneous and Maximization Tests of Fragrance Materials in guinea Pigs. Unpublished report from Givaudan Corporation. RIFM report number 6068. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1986. Delayed Contact Hypersensitivity Study of Methyl Octine Carbonate in guinea Pigs. Report to RIFM. RIFM report number 4466. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1988. Test to Evaluate the Sensitizing Potential of Methyl 2-nonynoate by Topical Application in the guinea Pig. Unpublished report from Christian Dior Parfums. RIFM report number 12547. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1988. Test to Evaluate the Phototoxic and Photoallergic Potentials, by Topical Applications of Methyl 2-nonynoate in the guinea-pig. Unpublished report from Christian Dior Parfums. RIFM report number 12925. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1988. Test to Evaluate the Sensitizing Potential by Topical Applications in the guinea-pig. Unpublished report from Christian Dior Parfums. RIFM report number 12926. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1989. Human Repeated Insult Patch Test of Methyl 2-octynoate and Methyl 2-nonynoate. RIFM report number 12367. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1989. Human Repeated Insult Patch Test of Methyl 2-nonynoate. RIFM report number 12369. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1989. Repeated Insult Patch Test of Methyl Octine Carbonate in Human Subjects. Report to RIFM. RIFM report number 27820. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1990. Repeat Insult Patch Test of Methyl 2-nonynoate in Human Subjects. RIFM report number 12454. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1990. Repeated Insult Patch Test of Methyl Octine Carbonate and T-2-Hexenal in Human Subjects. Report to RIFM. RIFM report number 27822. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1998. Ready biodegradability of methyl 2-nonynoate (methyl octine carbonate). Unpublished report from Givaudan. RIFM report number 56039. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1998. Partition Coefficient N-Octanol/water of Methyl 2-nonynoate (Methyl Octine Carbonate). Unpublished report from Givaudan. RIFM report number 56040. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1999. Inherent Biodegradability of Methyl 2-nonynoate (Methyl Octine Carbonate). Unpublished report from Givaudan. RIFM report number 56038. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2006. Investigation of the Relationship between Induction and Elicitiation Thresholds for Contact Allergy. RIFM report number 50101. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM report number 55663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Ready Biodegradability of Methyl 2-nonynoate (Methyl Octine Carbonate). Unpublished report from Givaudan. RIFM report number 66631. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015. Exposure Survey 08, October 2015.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Methyl 2-nonynoate (Methyl Octine Carbonate): Toxicity to the Pseudokirchneriella Subcapitata in a 72-hour Algal Growth Inhibition Test. Unpublished report from RIFM report number 71564. RIFM, Woodcliff Lake, NJ, USA.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Ryan, C.A., Gerberick, G.F., Cruse, L.W., Basketter, D.A., Lea, L., Blaikie, L., Dearman, R.J., Warbrick, E.V., Kimber, I., 2000. Activity of human contact allergens in the murine local lymph node assay. Contact Dermatitis 43 (2), 95–102.
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.
Urbisch, D., Mehling, A., Guth, K., Ramirez, T., Honarvar, N., et al., 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. Regul. Toxicol. Pharmacol. 71 (2), 337–351.
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.
Wild, D., King, M.T., Gocke, E., Eckhardt, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Food Chem. Toxicol. 21 (6), 707–719.