Food and Chemical Toxicology 134 (2019) 110826

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, methoxy dicyclopentadiene carboxaldehyde, CAS Registry Number 86803-90-9

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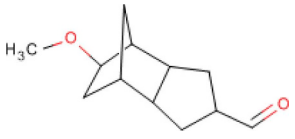
ARTICLE INFO

Keywords:
Genotoxicity
Repeated Dose, Developmental, and Reproductive Toxicity
Skin Sensitization
Phototoxicity/Photoallergenicity
Local Respiratory Toxicity
Environmental Safety

Version: 052919. This version replaces any previous versions.
Name: Methoxy dicyclopentadiene carboxaldehyde
CAS Registry Number: 86803-90-9



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https://doi.org/10.1016/j.fct.2019.110826
Received 8 July 2019; Accepted 16 September 2019
Available online 19 September 2019
0278-6915/

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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food

VoU - Volume of Use vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and 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.

Methoxy dicyclopentadiene carboxaldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methoxy dicyclopentadiene carboxaldehyde is not genotoxic. Data provided methoxy dicyclopentadiene carboxaldehyde a NESIL of 2500 μg/cm^2 for the skin sensitization endpoint. Data on methoxy dicyclopentadiene carboxaldehyde provide a calculated MOE > 100 for the repeated dose toxicity endpoint. The 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 (0.0015 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; methoxy dicyclopentadiene carboxaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methoxy dicyclopentadiene carboxaldehyde was not found 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. (RIFM, 1985; RIFM, 1995a)
Repeated Dose Toxicity: NOAEL = 250 mg/kg/day RIFM (1996a)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 2500 μg/cm^2. RIFM (1997)
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: Critical Measured Value: 40% (OECD 301D) (RIFM, 1995f)
Bioaccumulation: Screening-level: 25.24 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Fish LC50: 5.626 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 Fish LC50: 5.626 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.5626 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** Methoxy dicyclopentadiene carboxaldehyde
2. **CAS Registry Number:** 86803-90-9
3. **Synonyms:** 4,7-Methano-1H-indene-2-carboxaldehyde, octahydro-5-methoxy; 8-Methoxytricyclo[5.2.2.1]decane-4-carboxaldehyde; Scentenal; Methoxy dicyclopentadiene carboxaldehyde
4. **Molecular Formula:** $C_{12}H_{18}O_2$
5. **Molecular Weight:** 194.27
6. **RIFM Number:** 1251

2. Physical data

1. **Boiling Point:** 92–100 °C @ 2 mm, 542 ± 2 K @ 98.9–101 kPa (RIFM, 1995g), 277.55 °C (EPI Suite)
2. **Flash Point:** 125 ± 2 °C (RIFM, 1995h), > 212 °F/100 °C, 125 °C (GHS)
3. **Log K_{OW}:** 2.63 (EPI Suite)
4. **Melting Point**: < 253 ± 0.5 K (RIFM, 1995g), 42.05 °C (EPI Suite)
5. **Water Solubility:** 219.8 mg/L (EPI Suite)
6. **Specific Gravity:** 1.075–1.079 @ 25/25 °C, 1.0760 @ 20.0 ± 0.5 °C (RIFM, 1995g)
7. **Vapor Pressure:** 0.003 mm Hg 20 °C (FMA Database), 0.00446 mm Hg @ 25 °C (EPI Suite), 0.00248 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a refreshing sea breeze, watery, and floral odor

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **Maximum Concentration in Hydroalcoholics:** 0.038% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.00029 mg/kg/day or 0.021 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.0014 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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** 80% SAM
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. 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

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Methoxy dicyclopentadiene carboxaldehyde 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.

8. Reach dossier

Available; accessed 05/29/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for methoxy dicyclopentadiene carboxaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.00100
2	Products applied to the axillae	0.057
3	Products applied to the face/body using fingertips	1.2
4	Products related to fine fragrances	1.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.27
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.27

5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.27
5D	Baby cream, oil, talc	0.091
6	Products with oral and lip exposure	0.0010
7	Products applied to the hair with some hand contact	2.2
8	Products with significant ano-genital exposure (tampon)	0.091
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.1
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.1
10B	Aerosol air freshener	7.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.091
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	100

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 methoxy dicyclopentadiene carboxaldehyde, the basis was the reference dose of 2.5 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 2500 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, methoxy dicyclopentadiene carboxaldehyde does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Methoxy dicyclopentadiene carboxaldehyde was assessed in the BlueScreen assay and found negative in the presence of metabolic activation and positive in the absence of metabolic activation. However, these positive results were observed at cytotoxic concentrations (reduced the relative cell density to less than 80%) (RIFM, 2012). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material. The mutagenicity of methoxy dicyclopentadiene carboxaldehyde was assessed in a GLP-compliant Ames assay conducted in accordance with guidelines similar to OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with methoxy dicyclopentadiene carboxaldehyde in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1985). Under the conditions of the study, methoxy dicyclopentadiene carboxaldehyde was considered not mutagenic in bacteria.

The clastogenic activity of methoxy dicyclopentadiene carboxaldehyde was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with guidelines similar to OECD TG 474. The test material was administered in arachis oil via a single intraperitoneal injection to groups of male and female CD-1 albino mice. Doses of 187.5, 375, or 750 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1995a). Under the conditions of the study, methoxy dicyclopentadiene carboxaldehyde was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, methoxy dicyclopentadiene carboxaldehyde does not present a concern for genotoxic potential.

Additional References: RIFM, 1995b.

Literature Search and Risk Assessment Completed On: 05/22/17.

10.1.2. Repeated dose toxicity

The MOE for methoxy dicyclopentadiene carboxaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methoxy dicyclopentadiene carboxaldehyde for the repeated dose toxicity endpoint. A 4-week subchronic toxicity study was conducted in Crl:CD(SD)BR rats. Groups of 5 rats/sex/dose were administered the test material via gavage at doses of 0, 500, 750, or 1000 mg/kg/day daily in a 0.5% w/v carboxymethylcellulose vehicle. At 1000 mg/kg/day, there was a statistically significant rise in blood urea nitrogen in females and a higher specific gravity of the urine in males when compared to the controls. There was a statistically significant increase in the absolute and relative liver weights in all treated females when compared to the controls, but this was not apparent in males. There were no treatment-related macroscopic findings or any histopathological evidence; thus, the increased liver weights observed in females were considered to be associated with the metabolism of the test material and not of toxicological significance. Therefore, the NOAEL was considered to be 750 mg/kg/day, based on alterations in clinical chemistry parameters (RIFM, 1996a).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 750/3 or 250 mg/kg/day.

Therefore, the methoxy dicyclopentadiene carboxaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the methoxy dicyclopentadiene carboxaldehyde NOAEL in mg/kg/day by the total systemic exposure to methoxy dicyclopentadiene carboxaldehyde, 250/0.0014 or 178571.

In addition, the total systemic exposure to methoxy dicyclopentadiene carboxaldehyde (1.4 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.2.1.1. Derivation of reference dose (RfD). Section IX 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) and a reference dose of 2.5 mg/kg/day.

The RfD for methoxy dicyclopentadiene carboxaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 250 mg/kg/day by the uncertainty factor, 100 = 2.5 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: RIFM, 1996b.

Literature Search and Risk Assessment Completed On: 05/25/17.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on methoxy dicyclopentadiene carboxaldehyde or on any read-across materials. The total systemic exposure to methoxy dicyclopentadiene

Table 1
Data Summary for methoxy dicyclopentadiene carboxaldehyde.

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]
> 2500 [1]	Weak	2500 (DEP)	NA	12500	2500

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 2 significant figures.

carboxaldehyde is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on methoxy dicyclopentadiene carboxaldehyde or on any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. When correcting for skin absorption (see Section IV), the total systemic exposure to methoxy dicyclopentadiene carboxaldehyde (1.4 μg/kg/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 endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/17.

10.1.4. Skin sensitization

Based on the available data, methoxy dicyclopentadiene carboxaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 2500 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, methoxy dicyclopentadiene carboxaldehyde is considered to be a weak skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD Toolbox v3.4). Methoxy dicyclopentadiene carboxaldehyde was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and human cell line activation test (h-CLAT) (RIFM unpublished results). However, in a murine local lymph node assay (LLNA), methoxy dicyclopentadiene carboxaldehyde was found to be negative up to a maximum tested concentration of 10%, which resulted in a stimulation index (SI) of 2.2 (RIFM, 2001). In a guinea pig maximization test, methoxy dicyclopentadiene carboxaldehyde presented reactions indicative of sensitization (RIFM, 1994). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 2500 μg/cm^2 of methoxy dicyclopentadiene carboxaldehyde in diethyl phthalate (DEP), no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 1997). Based on the available data, summarized in the current IFRA Standard, methoxy dicyclopentadiene carboxaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 2500 μg/cm^2 (Table 1). Section IX 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) and a reference dose of 2.5 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/16/17.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for methoxy dicyclopentadiene carboxaldehyde in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, methoxy dicyclopentadiene carboxaldehyde does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for methoxy dicyclopentadiene carboxaldehyde were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/22/19.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on methoxy dicyclopentadiene carboxaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.021 mg/day. This exposure is 22.4 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: 02/26/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methoxy dicyclopentadiene carboxaldehyde 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, methoxy dicyclopentadiene carboxaldehyde 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 methoxy dicyclopentadiene carboxaldehyde as possibly being 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.

10.2.1.1. Risk assessment. Based on the current VoU (2015), methoxy dicyclopentadiene carboxaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Biodegradation. RIFM, 1995f: A ready biodegradation study was conducted using the closed bottle test according to the OECD 301D method. After 28 days, biodegradation of 40% was observed.

10.2.1.3. Ecotoxicity. RIFM, 1995c: The 96-h acute toxicity of the test material was determined using juvenile rainbow trout following the OECD 203 guidelines under semi-static conditions. The LC50 was calculated to be 42 mg/L.

RIFM, 1995d: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was calculated to be 5.5 mg/L.

RIFM, 1995e: The effects of the test material on the growth of the green algae *Scenedesmus subspicatus* were studied according to the OECD 201 method. The 72-h EC50 was calculated to be 1.0 mg/L.

10.2.1.4. Other available data. Methoxy dicyclopentadiene carboxaldehyde has been registered under REACH with no additional data at this time.

10.2.2. Risk assessment refinement

Since methoxy dicyclopentadiene carboxaldehyde has passed the screening criteria, measured data is included in this document 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)**	74.18			1000000	0.07418	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.626	6.635	11.67	10000	0.5626	Aldehydes (mono)
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	46.99	28.28	26.79			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	2.63	2.63
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	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 0.5626 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 04/01/19.

11. 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 05/30/19.

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.

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.

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/.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

RIFM (Research Institute for Fragrance Materials, Inc), 1985. Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Methoxy Dicyclopentadiene Carboxaldehyde. Unpublished report from Firmenich Incorporated. RIFM report number 30027. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1994. Skin Sensitization Study of Methoxy Dicyclopentadiene Carboxaldehyde in guinea Pigs. Unpublished report from Firmenich Incorporated. RIFM report number 30024. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995a. Micronucleus Test of Methoxy Dicyclopentadiene Carboxaldehyde in the Mouse. Unpublished report from Firmenich Incorporated. RIFM report number 30029. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995b. Chromosome Aberration Test in Human Lymphocytes of Methoxy Dicyclopentadiene Carboxaldehdye in Vitro. Unpublished report from Firmenich Incorporated. RIFM report number 30028. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995c. Acute Toxicity of Methoxy Dicyclopentadiene Carboxaldehyde in Rainbow Trout (oncorhynchus Mykiss). Unpublished report from Firmenich Incorporated. RIFM report number 30032. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995d. Acute Toxicity of Methoxy Dicyclopentadiene Carboxaldehyde to Daphnia Magna. Unpublished report from Firmenich Incorporated. RIFM report number 30033. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995e. Algal Inhibition Test of Methoxy Dicyclopentadiene Carboxaldehyde. Unpublished report from Firmenich Incorporated. RIFM report number 30034. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995f. Assessment of the Ready Biodegradability (Closed Bottle Test) of Methoxy Dicyclopentadiene Carboxaldehyde. Unpublished report from Firmenich Incorporated. RIFM report number 30036. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995g. Determination of General Physico-Chemical Properties of Methoxy Dicyclopentadiene Carboxaldehyde. Unpublished report from Firmenich Incorporated. RIFM report number 30037. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1995h. Determination of Flash Point of Methoxy Dicyclopentadiene Carboxaldehyde. Unpublished report from Firmenich Incorporated. RIFM report number 30039. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1996a. 4 Week Oral (Gavage) Toxicity Study of Methoxy Dicyclopentadiene Carboxaldehyde in the Rat. Unpublished report from Firmenich Incorporated. RIFM report number 30030. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1996b. 7-Day Oral (Gavage) Dose Range Finding Study of Methoxy Dicyclopentadiene Carboxaldehyde in the Rat. Unpublished report from Firmenich Incorporated. RIFM report number 30031. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1997. Repeated Insult Patch Test of Methoxy Dicyclopentadiene Carboxaldehyde in Human Subjects. Unpublished report from Firmenich Incorporated. RIFM report number 30026. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2001. Murine Local Lymph Node Assay with Methoxy Dicyclopentadiene Carboxaldehyde. Unpublished report from Firmenich SA. RIFM report number 42120. 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), 2012. Report on the Testing of 21 Compounds in BlueScreen HC Assay (-/+ S9 Metabolic Activation). Unpublished report from Firmenich. RIFM report number 65264. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc)., 2015. Exposure Survey 07. May 2015.

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.

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.