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RIFM fragrance ingredient safety assessment, *cis*-3-hexenyl methyl carbonate, CAS Registry Number 67633-96-9

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ABSTRACT

Abstract The following paper presents the method of determination of the percolation threshold in cement composites with expanded graphite by impedance spectroscopy. Most of the applications of cement composites with conductive additives require exceeding the percolation threshold. The ionic conductivity of cement matrix below the percolation threshold has a major impact on the conductivity of the composite, as a result, it significantly hinders the exploitation of these composites. The electric properties of cement composites with expanded graphite were evaluated by DC measurements and impedance spectroscopy (IS). Based on Nyquist plots, two equivalent circuits were adopted for the composites. Next, the values of capacitance and inductance of cement composites with expanded graphite were calculated from the fitted equivalent circuits. The analysis of the results shows that the percolation threshold occurs when the reactance of the composite changes from captative to inductive. Comparison between the values of percolation threshold obtained from DC measurements and IS shows that the method is effective for cement composites with conductive additives.

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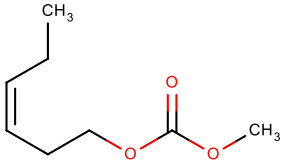


Name: *cis*-3-Hexenyl methyl carbonate
CAS Registry Number: 67633-96-9

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

(*continued on next column*)

(*continued*)

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.

cis-3-Hexenyl methyl carbonate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *cis*-3-hexenyl methyl carbonate is not genotoxic. Data on read-across materials *cis*-3-hexenol (CAS # 928-96-1) and methanol (CAS # 67-56-1) provide a calculated margin of exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data provided *cis*-3-hexenyl methyl carbonate a No Expected Sensitization Induction Level (NESIL) of 1300 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *cis*-3-hexenyl methyl carbonate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to *cis*-3-hexenyl methyl carbonate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *cis*-3-hexenyl methyl carbonate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2006; RIFM, 2018)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day.	US EPA (2013)
Reproductive Toxicity: Developmental toxicity NOAEL: 300 mg/kg/day, Fertility NOAEL: 1000 mg/kg/day.	(ECHA REACH Dossier: cis-Hex-3-en-1-ol; ECHA, 2013)
Skin Sensitization: NESIL = 1300 μg/cm^2.	RIFM (2012a)
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: 101% (OECD 301C Modified MITI test)	RIFM (2015)
Bioaccumulation:	
Screening-level: 19.93 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-hr Algae EC50: 8.721 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, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 8.721 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.8721 μg/L	

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

1. Identification

1. **Chemical Name:** *cis*-3-Hexenyl methyl carbonate
2. **CAS Registry Number:** 67633-96-9
3. **Synonyms:** Carbonic acid, 3-hexenyl methyl ester, (Z)-; Liffarome; Methyl *cis*-3-hexenyl carbonate; *cis*-3-Hexenyl carbonate; Hex-3-en-1-yl methyl carbonate; Leafovert; *cis*-3-Hexenyl methyl carbonate
4. **Molecular Formula:** $C_8H_{14}O_3$
5. **Molecular Weight:** 158.19
6. **RIFM Number:** 1322

7. **Stereochemistry:** *cis* Isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 213 °C (EPI Suite)
2. **Flash Point:** 70 °C (Globally Harmonized System)
3. **Log K_{OW}:** Log Pow = 2.6 (RIFM, 2013), 2.47 (EPI Suite)
4. **Melting Point**: −60.84 °C (EPI Suite)
5. **Water Solubility:** 537.8 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.125 mm Hg at 20 °C (EPI Suite v4.0), 0.3 mm Hg 20 °C (Fragrance Materials Association), 0.187 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid (ECHA, 2017)

3. Volume of use (Worldwide band)

1. 100–1000 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:** 0.035% (RIFM, 2017b)
2. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0092 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.00095 mg/kg/day (RIFM, 2017b)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** *cis*-3-Hexenol (CAS # 928-96-1) and methanol (67-56-1)
   c. **Reproductive Toxicity:** *cis*-3-Hexenol (CAS # 928-96-1) and methanol (67-56-1)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

cis-3-Hexenyl methyl carbonate is not reported to occur in foods 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 11/02/19 (ECHA, 2017).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for *cis*-3-hexenyl methyl carbonate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.10
2	Products applied to the axillae	0.030
3	Products applied to the face/body using fingertips	0.60
4	Products related to fine fragrances	0.56
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.14
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.14
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.14
5D	Baby cream, oil, talc	0.047
6	Products with oral and lip exposure	0.33
7	Products applied to the hair with some hand contact	1.1
8	Products with significant ano-genital exposure (tampon)	0.047
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.1
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.9
10B	Aerosol air freshener	3.9
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.047
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 *cis*-3-hexenyl methyl carbonate, the basis was the reference dose of 3.0 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1300 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *cis*-3-hexenyl methyl carbonate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of *cis*-3-hexenyl methyl carbonate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations using the pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *cis*-3-hexenyl methyl carbonate in dimethyl sulfoxide (DMSO) at concentrations up to 1250 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, 2006). Under the conditions of the study, *cis*-3-hexenyl methyl carbonate was not mutagenic in the Ames test.

The clastogenic activity of *cis*-3-hexenyl methyl carbonate 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 *cis*-3-hexenyl methyl carbonate in DMSO at concentrations up to 1580 μg/mL in a dose range finding (DRF) study, and micronuclei analysis 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 *cis*-3-Hexenyl methyl carbonate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels under 24-h treatment without S9 and up to maximum concentration in 4-h treatment with and without S9 activation system (RIFM, 2018). Under the conditions of the study, *cis*-3-hexenyl methyl carbonate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, *cis*-3-hexenyl methyl carbonate does not present a concern for genotoxic.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/28/21.

11.1.2. Repeated dose toxicity

The MOE for *cis*-3-hexenyl methyl carbonate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *cis*-3-hexenyl methyl carbonate. Read-across materials *cis*-3-hexenol (CAS # 928-96-1; see Section VI) and methanol (CAS # 67-56-1; see Section VI) have sufficient repeated dose toxicity data.

In a subchronic repeated dose toxicity study, *cis*-hex-3-en-1-ol (synonym for *cis*-3-hexenol) was administered via drinking water to groups of 15 SPF-derived CFE weanling rats/sex/dose at doses of 0, 310, 1250, or 5000 ppm for 98 days. Observations included mortality, clinical signs, body weight, food intake, and water consumption. Gross pathology, organ weight, and histopathology were conducted, and hematological and urinary analysis parameters were examined at weeks 6 and 14. There was a decrease in hemoglobin concentration among females at week 6, but no significant changes in hematocrit values or in erythrocyte or reticulocyte counts were reported. This was not considered to be significant since this finding was not observed at week 14 or in any of the male animals. An increase in specific gravity and a decrease in the volume of urine produced during the first 2 h after a water load were observed in males at the highest dose after 14 weeks; this effect was not seen in week 6 treated males or in females after 6 or 14 weeks of treatment. Based on no treatment-related adverse effects up to the highest dose, the NOAEL was considered to be 5000 ppm or 500 mg/kg/day (Gaunt, 1969). In another study (28 days), following the OECD 422/GLP guidelines, test material *cis*-hex-3-en-1-ol was administered via oral gavage to groups of 11 RCCHan:WIST (SPF) rats/sex/dose at doses of 0, 100, 300, or 1000 mg/kg/day. The male and female rats were treated for a total of 41 and 53 days, respectively. Mortality was reported among the highest-dose group animals; 1 male and 4 female rats were found dead at different points. The cause of death was considered by the authors to be aspiration during the gavage procedures and not related to the systemic toxicity of the test material**. The NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested** (ECHA, 2013). The most conservative NOEL of 125 mg/kg/day obtained from the 98-day study was considered for the safety assessment of 3-hexen-1-ol (isomer unspecified).

In a non-guideline repeated dose toxicity study, 5 Sprague Dawley CD rats/sex/dose were exposed to methanol via whole-body inhalation at doses of 0, 500, 2000, and 5000 ppm for 4 weeks (6 h/day, 5 days/week). Parameters included ophthalmoscopic exam, body weight, clinical signs, organ weights, histopathology, and survival. No treatment-related mortality occurred throughout the study period. Nasal and eye discharge (mucoid, nasal, red nasal, lacrimation) was noted in rats from all treatment groups; however, only mucoid nasal discharge appeared to be dose-related. No treatment-related effects were observed on body weight, ocular health, or histopathology. Spleen weights were increased in females at the mid dose (2000 ppm) but not at the high dose, so the effect was not dose-dependent. No other organ effects were reported. Due to the absence of adverse effects up to the highest dose, the NOAEC of this study was considered to be 5000 ppm. Using standard minute volume and body weight values for male and female Sprague Dawley rats, the calculated NOAEL for repeated dose toxicity is 1699 mg/kg/day (Andrews, 1987).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1699/3 or 566 mg/kg/day. In an EPA-conducted repeated dose study, 30 Sprague-Dawley rats/sex/dose were administered methanol via gavage at doses of 0, 100, 500, and 2500 mg/kg/day for 90 days (10 rats/sex/dose were euthanized after 42 days). Parameters included body weights, food consumption, clinical signs of toxicity, hematology, serum chemistry, urinalysis tests, gross and microscopic evaluations, and organ histopathology. There was no treatment-related mortality throughout the study period. Additionally, no treatment-related effects were reported in bodyweight gain, food consumption, or gross or microscopic evaluations. All treatment-related effects were reported in high-dose (2500 mg/kg/day) males and females. These effects included statistically significant increases in serum alanine transaminase (ALT) and serum alkaline phosphatase (SAP). Increased liver weights were also reported in this group but were not statistically significant and were not accompanied by supportive histopathologic lesions. Significantly decreased brain weights were also reported at terminal sacrifice. Higher incidence of colloid in the hypophyseal cleft of the pituitary gland was reported (13/20 high-dose males versus 0/20 control males, 9/20 high-dose females versus 3/20 high-dose females). Based biochemical changes, decreased brain weights, and histopathology, the NOAEL of this study was determined to be 500 mg/kg/day. The most conservative NOAEL was obtained from the 90-day EPA-conducted repeat dose study and determined to be 500 mg/kg/day.

Because there was only 1 study that found treatment-related adverse effects across all of the metabolites, the NOAEL was obtained from the 90-day EPA-conducted study on methanol (500 mg/kg/day). See Table 1 below for additional data. **Therefore, the *cis*-3-hexenyl methyl carbonate MOE for the repeated dose toxicity endpoint can be calculated by dividing the NOAEL for methanol in mg/kg/day by**

Table 1
Additional studies.

Material	Duration in Detail	GLP/Guideline	No. of Animals/ Dose (Species, Strain, Sex)	Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEC	Justification of NOAEL/LOAEL/NOEL	References
Methanol	104 weeks	Non-guideline and non-GLP	Sprague Dawley rats (100/sex/dose)	Drinking water	0, 500, 5000, 20000 ppm	NOAEL = 20000 ppm	No pattern of chemical-related signs of toxicity	US EPA (2013)
Methanol	4 weeks	Non-guideline and non-GLP	Sprague Dawley rats (5/sex/dose)	Inhalation	0, 500, 2000, 5000 ppm	NOAEL = 5000 ppm	No chemical-related changes in gross pathology, histopathology, ophthalmoscopy	Andrews (1987)

the total systemic exposure to *cis*-3-hexenyl methyl carbonate, 500/0.00095, or 526316.

In addition, the total systemic exposure to *cis*-3-hexenyl methyl carbonate (0.95 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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, 1974.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.3. Reproductive toxicity

The MOE for *cis*-3-hexenyl methyl carbonate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on *cis*-3-hexenyl methyl carbonate. Read-across materials *cis*-3-hexenol (CAS # 928-96-1; see Section VI) and methanol (CAS # 67-56-1; see Section VI) have sufficient reproductive toxicity data. The hydrolysis product methanol has been reviewed by multiple agencies, including the US EPA (US EPA, 2013), NICNAS (NICNAS, 2013), OECD (OECD, 2004), and CIR (CIR, 2001). The CIR panel concluded that methanol is safe as used to denature ethyl alcohol when used in cosmetic products (CIR, 2001). Furthermore, methanol occurs naturally in the human body as a product of metabolism and through intake of fruits, vegetables, and alcoholic beverages. The background blood methanol levels in healthy humans measured following the restriction of methanol-producing foods in the diet were found to be 0.25–5.2 mg/L (US EPA, 2013). Exposure to methanol via hydrolysis of *cis*-3-hexenyl methyl carbonate is not expected to adversely affect the background levels of methanol levels in humans, and hence, is not a concern for human health safety. In an OECD 422/GLP study, groups of 11 RCCHan:WIST (SPF) rats/sex/dose were administered the test material *cis*-hex-3-en-1-ol via gavage at doses of 0, 100, 300, or 1000 mg/kg/day. The male and female rats were treated for a total of 41 and 53 days, respectively. There were no effects on reproductive parameters, which included precoital times, fertility index, conception rate, and mean number of corpora lutea per dam. There were no effects on litter size, birth index, or sex ratio. The mean postnatal loss was 1.6%, 1.2%, 1.6%, and 9.6% in dose groups 0, 100, 300, and 1000 mg/kg/day, respectively. The cause of the slightly higher postnatal loss in the 1000 mg/kg/day group was the loss of 7 pups on days 2 and 3 post-partum for a single dam; this isolated occurrence was considered to be incidental. The Expert Panel for Fragrance Safety* concluded that although the finding in 1 litter from 1 dam is most likely incidental, the more conservative NOAEL of 300 mg/kg/day should be selected for developmental toxicity. Hence, based on higher postnatal loss seen at 1000 mg/kg/day, the NOAEL for developmental toxicity was considered to be 300 mg/kg/day, while NOAEL for fertility was 1000 mg/kg/day, which was the highest dose tested (ECHA, 2013).

Therefore, the *cis*-3-hexenyl methyl carbonate MOE for the developmental endpoint can be calculated by dividing the *cis*-hex-3-en-1-ol NOAEL in mg/kg/day by the total systemic exposure to *cis*-3-hexenyl methyl carbonate, 300/0.00095, or 315789.

The *cis*-3-hexenyl methyl carbonate MOE for the fertility can be calculated by dividing the *cis*-hex-3-en-1-ol NOAEL in mg/kg/day by the total systemic exposure to *cis*-3-hexenyl methyl carbonate, 1000/0.00095, or 1052632.

In addition, the total systemic exposure to *cis*-3-hexenyl methyl carbonate (0.95 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint for a Cramer Class I material at the current level of use.

Derivation of reference dose (RfD): Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 3 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for *cis*-3-hexenyl methyl carbonate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 300 mg/kg/day by the uncertainty factor, 100 = 3 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/21.

11.1.4. Skin sensitization

Based on the existing data, *cis*-3-hexenyl methyl carbonate is considered a skin sensitizer with a defined NESIL of 1300 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, *cis*-3-hexenyl methyl carbonate is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.3). In a murine local lymph node assay (LLNA), *cis*-3-hexenyl methyl carbonate was found to be sensitizing with an EC3 value of 71% (17750 μg/cm^2) (ECHA, 2017, 001 Key study; RIFM, 2017a). A guinea pig Buehler test did not present reactions indicative of sensitization at 2.5% (RIFM, 1979). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2.5% or 1390 μg/cm^2 *cis*-3-hexenyl methyl carbonate in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2012a). In another CNIH with 100% or 77519 μg/cm^2 of *cis*-3-hexenyl methyl carbonate, no reactions indicative of sensitization were observed in any of the 37 volunteers (RIFM, 1966). Similarly, in another CNIH with 2.5% or 1250 μg/cm^2 of *cis*-3-hexenyl methyl carbonate in SDA 39C alcohol, no reactions indicative of sensitization were observed in any of the 53 volunteers (RIFM, 1980).

Based on weight of evidence (WoE) from structural analysis as well as animal and human studies, *cis*-3-hexenyl methyl carbonate is a sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 1300 μg/cm^2 (Table 2). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference

Table 2
Data Summary for *cis*-3-hexenyl methyl carbonate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
17750 [1]	Weak	1390	NA	NA	1300

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

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

dose of 3 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *cis*-3-hexenyl methyl carbonate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *cis*-3-hexenyl methyl carbonate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, *cis*-3-hexenyl methyl carbonate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *cis*-3-hexenyl methyl carbonate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on *cis*-3-hexenyl methyl carbonate. Based on the Creme RIFM Model, the inhalation exposure is 0.0092 mg/day. This exposure is 152.2 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *cis*-3-hexenyl methyl carbonate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *cis*-3-hexenyl methyl carbonate 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 *cis*-3-hexenyl methyl carbonate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *cis*-3-Hexenyl methyl carbonate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2015: The ready biodegradability of the test material was evaluated using the Modified MITI test according to the OECD 301C guideline. Biodegradation of 101% was observed after 28 days.

RIFM, 2012b: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 79% was observed after 28 days.

RIFM, 2011: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. The mean biodegradation of 87% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. *cis*-3-Hexenyl methyl carbonate has been registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Since *cis*-3-hexenyl methyl carbonate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	2.6	2.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
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 0.8721 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: 05/05/21.

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
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/18/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112648.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	64.15			1000000	0.06415	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	11.180	22.089	8.721	10000	0.8721	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	48.754	28.922	25.819			Neutral Organic SAR (Baseline toxicity)

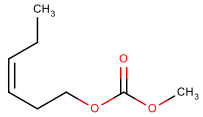
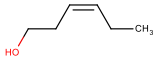
Appendix

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 Chemicals 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, 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).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	*cis*-3-Hexenyl methyl carbonate	*cis*-3-Hexenol	Methanol
CAS No.	67633-96-9	928-96-1	67-56-1
Structure			
Similarity (Tanimoto Score)		0.36	0.07
Read-across Endpoint		• Repeated Dose Toxicity • Reproductive toxicity	• Repeated Dose Toxicity • Reproductive toxicity
Molecular Formula	$C_8H_{14}O_3$	$C_6H_{12}O$	CH_4O
Molecular Weight	158.19	100.16	32.04
Melting Point (°C, EPI Suite)	−60.84	−38.47	−97.60
Boiling Point (°C, EPI Suite)	213.00	156.50	64.70
Vapor Pressure (Pa @ 25°C, EPI Suite)	24.93	124.92	16931.89
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.47	1.61	−0.77
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.38E+002	1.60E+004	1.00E+006
J_{max} (μg/cm^2/h, SAM)	75.861	446.293	4753.139
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.28E+002	1.57E+000	4.61E-001
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Not categorized
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)	• Toxicant (moderate reliability)	• Toxicant (moderate reliability)
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	No Metabolites

Summary

There are insufficient toxicity data on *cis*-3-hexenyl methyl carbonate (CAS # 67633-96-9). 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, *cis*-3-hexenol (CAS # 928-96-1) and methanol (CAS # 67-56-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target *cis*-3-hexenyl methyl carbonate (CAS # 67633-96-9) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to *cis*-3-hexenol (CAS # 928-96-1) and methanol (CAS # 67-56-1) in the first step with 0.95 probability. Hence, *cis*-3-hexenol (CAS # 928-96-1) and methanol (CAS # 67-56-1) can be used as read-across analogs for the target material. Read-across analogs *cis*-3-hexenol (CAS # 928-96-1) and methanol (CAS # 67-56-1) were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification was provided.

Conclusions

- Read-across alcohols *cis*-3-hexenol (CAS # 928-96-1) and methanol (CAS # 67-56-1) were used as read-across analogs for the target ester *cis*-3-hexenyl methyl carbonate (CAS # 67633-96-9) for the repeated dose and reproductive toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohols and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o The structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The read-across metabolites have toxicant alerts the for developmental toxicity endpoint. The data described in the developmental toxicity section show that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by the data.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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