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Short review

RIFM fragrance ingredient safety assessment, Methyl hexyl oxo cyclopentanone carboxylate, CAS Registry Number 37172-53-5

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1. Identification

1. **Chemical Name:** Methyl hexyl oxo cyclopentanone carboxylate
2. **CAS Registry Number**: 37172-53-5
3. Synonyms: Dihydro isojasmonate; Jasmopol; Methyl hexyl oxo cyclopentanone carboxylate; Methyl 2-hexyl-3-oxocyclopentanecarboxylate; Cyclopentanecarboxylic acid, 2-hexyl-3-oxo-, methyl ester; Dihydrojasmonate; ﾒﾁﾙ=2-ﾍｷｼﾙｰ 3-ｵｷｿｼｸﾛﾍﾟﾝﾀﾝｶﾙﾎﾞｷｼﾗｰﾄ
4. **Molecular Formula**: $C^{13}H^{22}O^3$
5. **Molecular Weight**: 226.32
6. **RIFM Number**: 1168

2. Physical data

1. **Boiling Point**: 296 C (570 K) [RIFM, 2008a], 309.32 °C [EPI Suite]
2. **Flash Point**: >200 °F; CC [FMA database]

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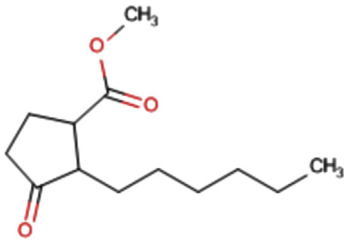
Version: 112816. This version replaces any previous versions.
Name: Methyl hexyl oxo cyclopentanone carboxylate
CAS Registry Number: 37172-53-5



Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile** - The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF - Assessment Factor
BCF - Bioconcentration Factor
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultra Violet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WOE - Weight of Evidence

3.**Log K_{OW}**: 2.98 [EPI Suite], log Pow = 3.2 (HPLC Method) [RIFM, 2008a]
4. **Melting Point**: 73.64 °C [EPI Suite]
5. **Water Solubility:** 91.72 mg/L [EPI Suite]
6. **Specific Gravity:** 0.99100 to 0.99900 @ 25 °C*
7. **Vapor Pressure**: 0.000216 mm Hg @ 20 °C [EPI Suite 4.0], 0.000412 mm Hg @ 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 to pale yellow clear liquid with a medium green jasmine, floral, fresh, oily, and herbal odor (Luebke, William tgsc, 1989)

** http://www.thegoodscentscompany.com/data/rw1027931.htmlretrieved 07/15/14.

3. Exposure

1. **Volume of Use (worldwide band)**: 10–100 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics**: 0.65% (IFRA, 2008)
3. **97.5**th **Percentile**: 2.34% (IFRA, 2008)
4. **Dermal Exposure***: 0.0596 mg/kg/day (IFRA, 2008)
5. **Oral Exposure**: Not available
6. **Inhalation Exposures****: 0.0036 mg/kg/day or 0.22 mg/day (IFRA, 2008)
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.0596 mg/kg/day x 45.9% absorption) + 0.0036 mg/kg/day = 0.031 mg/kg/day

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

RIFM's Expert Panel* concludes that this material is safe under the limits 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog methyl dihydrojasmonate (CAS # 24851-98-7) show that this material is not genotoxic, it does not have skin sensitization potential, and provided a MOE > 100 for the repeated dose, developmental and reproductive, and local respiratory toxicity endpoints. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2007; RIFM, 1998)

Repeated Dose Toxicity: NOEL = 100 mg/kg/day (RIFM, 2007)

Developmental and Reproductive Toxicity: NOAEL = 120 mg/kg/day and 300 mg/kg/day, respectively. (Politano et al., 2008; Politano et al., 2008; RIFM, 2012)

Skin Sensitization: Not sensitizing. (ECHA Dossier, accessed 05/05/2014; RIFM, 1971a; RIFM, 2003b; RIFM, 2004a; RIFM, 2005; RIFM, 1971b; RIFM, 1971c; RIFM, 1976; RIFM, 1972)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)

Local Respiratory Toxicity: NOEC = 93 mg/m^3 (RIFM, 2013)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 86% (OECD 301D) (RIFM, 1996)

Bioaccumulation: Screening Level: 42.65 L/kg (EpiSuite ver 4.1)

Ecotoxicity: Screening Level: 96 h Algae EC50: 5.569 mg/L (EpiSuite ver 4.1)

Conclusion: Not PBT as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 96 h Algae EC50: 5.569 mg/L (EpiSuite ver 4.1)

RIFM PNEC is: 0.5569 μg/L

•**Revised PEC/PNECs (2011 IFRA Volune of Use):** North America and Europe <1

4. Derivation of systemic absorption

1. **Dermal**: 45.9%, read-across from 14C-methyl dihydrojasmonate (CAS # 24851-98-7)

RIFM, 2001b **(data also available in** Isola and Api, 2002**):** An *in vitro* human percutaneous absorption study was conducted with read across material ^{14}C-methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5). The study was designed to determine the *in vitro* skin penetration rate and distribution of the radiolabelled test material at 20 μl/cm^2 of a 1% solution in ethanol. Franz-type diffusion cells were used under non-occlusive conditions. Samples from the receptor fluid were taken at 2, 8, 24, 36, and 48 h and were analyzed by liquid scintillation. The epidermal membranes were tape stripped 10 times and were grouped, solubilized, and analyzed. The evaporative loss of the test material over a 48 h period was assessed using PTFE sheets mounted in the diffusion cells. The PTFE sheets were removed at 1, 2, 4, 8, 24, and 48 h after dosing and washed with solvent. After 24 and 36 h, the receptor phase level of methyl dihydrojasmonate was 30.79% and 40.12% of applied dose, respectively. Following 48 h exposure, 45.9± 3.5% of the applied dose of methyl dihydrojasmonate had permeated into the receptor phase. The total recovery of methyl dihydrojasmonate from the PTFE surfaces at 48 h was 86% of the applied dose, indicating losses through evaporation from the PTFE surface of 14%. The levels of methyl dihydrojasmonate in the surface wipe and donor chamber wash were 14.0 ± 1.8 μg/cm^2 and 20.2 ± 2.7 μg/cm^2, respectively. Overall recovery (surface wipe, tape strips, remaining epidermis, receptor phase and donor chamber) of methyl dihydrojasmonate was 65.8± 2.8% of the applied dose.

2. **Oral:** Data not available - not considered.

3. **Inhalation**: Assumed 100%

4. **Total:** Dermal (45.9%) + Inhalation (assume 100%) absorbed = (0.0596 mg/kg/day x 45.9%) + 0.0036 mg/kg/day = 0.031 mg/kg/day

5. Computational toxicology evaluation

1. Cramer Classification: Class II, Intermediate (Expert Judgment)

Expert Judgement	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	II	III

*See Appendix below for explanation.

2. **Analogs Selected**:

a. Genotoxicity: Methyl dihydrojasmonate (CAS # 24851-98-7)

b. Repeated Dose Toxicity: Methyl dihydrojasmonate (CAS # 24851-98-7)

c. Developmental and Reproductive Toxicity: Methyl dihydrojasmonate (CAS # 24851-98-7)

d. Skin Sensitization: Methyl dihydrojasmonate (CAS # 24851-98-7)

e. Phototoxicity/Photoallergenicity: None

f. Local Respiratory Toxicity: Methyl dihydrojasmonate (CAS # 24851-98-7)

g. Environmental Toxicity: None

3. Read-across Justifications: See Appendix below

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)

Methyl hexyl oxo cyclopentanone carboxylate 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 11/28/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, methyl hexyl oxo cyclopentanone carboxylate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of methyl hexyl oxo cyclopentanone carboxylate was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. Methyl hexyl oxo cyclopentanone carboxylate was tested at concentrations ranging from 33 to 2000 μg/plate in the presence and absence of S9 mix in *Salmonella typhimurium* strains TA1535, TA1537 and TA100. Methyl hexyl oxo cyclopentanone carboxylate was tested at a concentration range of 33–3330 μg/plate in the presence and absence of S9 mix in tester strains TA 98 and *Escherichia coli* strain WP2uvrA. No significant increase in the number of revertant colonies was observed in the strains at any concentration tested (RIFM, 2008b). Under the conditions of the study, methyl hexyl oxo cyclopentanone carboxylate is not considered mutagenic in the Ames test.

There are no studies assessing the clastogenic potential of methyl hexyl oxo cyclopentanon carboxylate, however, the material methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) was identified as suitable to use for read across. The clastogenic activity of methyl dihydrojasmonate was assessed in an *in vivo* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 474. Groups of five male and female ICR mice were dosed with methyl dihydrojasmonate in corn oil via a single intraperitoneal injection at the concentrations of 280, 560 and 1120 mg/kg body weight. No significant increases in micronucleated polychromatic erythrocytes were observed at 24 or 48 h compared to vehicle control groups (RIFM, 1998). Under the conditions of the study, methyl dihydrojasmonate was not considered to be clastogenic in the *in vivo* micronucleus test and this can be extended to methyl hexyl oxo cyclopentanone carboxylate. Additionally, RIFM's Expert Panel and Adjunct Reproduction Advisory Group has reviewed the SAR category Ketone/Cyclopentanones & Cyclopentenones/Cyclopentanones/Keto Esters, and concluded that they do not have a genotoxic potential (Belsito et al., 2012).

Based on the available data, methyl hexyl oxo cyclopentanone carboxylate does not present a concern for genotoxic potential.

Additional References: RIFM, 2000c; RIFM, 2000d; RIFM, 2001a; RIFM, 1979; RIFM, 1978; RIFM, 1988; RIFM, 2001c; Bhatia et al., 2008.

Literature Search and Risk Assessment Completed on: 05/08/2014.

10.1.2. Repeated dose toxicity

The margin of exposure for methyl hexyl oxo cyclopentanone carboxylate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl hexyl oxo cyclopentanone carboxylate. Read across material, methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) has an OECD 408 dietary 90-day subchronic toxicity study conducted in rats. The NOEL was determined to be 100 mg/kg/day, the highest dose tested (RIFM, 2000b). **Therefore, the methyl hexyl oxo cyclopentanone carboxylate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl dihydrojasmonate NOEL in mg/kg/day by the total systemic exposure to methyl hexyl oxo cyclopentanone carboxylate, 100/0.031 or 3226.**

Additional References: Scognamiglio et al., 2012b; Belsito et al., 2012; RIFM, 2000a; RIFM, 2013; Singal et al., 2014; Scognamiglio et al., 2012a

Literature Search and Risk Assessment Completed on: 05/06/2014

10.1.3. Developmental and reproductive toxicity

The margin of exposure for methyl hexyl oxo cyclopentanone carboxylate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on methyl hexyl oxo cyclopentanone carboxylate. Read across material, methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) has a gavage developmental toxicity study in rats. The NOAEL for developmental toxicity was determined to be 120 mg/kg/day, the highest dose tested (Politano et al., 2008; RIFM, 2007). **Therefore, the methyl hexyl oxo cyclopentanone carboxylate MOE for the developmental toxicity endpoint can be calculated by dividing the methyl dihydrojasmonate NOAEL in mg/kg/day by the total systemic exposure to methyl hexyl oxo cyclopentanone carboxylate, 120/0.031 or 3871.**

There are no reproductive toxicity data on methyl hexyl oxo cyclopentanone carboxylate. Read across material, methyl dihydrojasmonate (CAS # 24851-98-7) has an OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats. The NOAELs for reproductive toxicity were determined to be 1000 mg/kg/day in males, the highest dose tested, and 300 mg/kg/day in females, based on decreased gestational bodyweight gain and decreased

pup bodyweights on day 0 (RIFM, 2012). **Therefore, the methyl hexyl oxo cyclopentanone carboxylate MOE for the reproductive toxicity endpoint can be calculated by dividing the methyl dihydrojasmonate NOAEL in mg/kg/day by the total systemic exposure to methyl hexyl oxo cyclopentanone carboxylate, 300/0.031 or 9677.**

Additional References: Scognamiglio et al., 2012b; Belsito et al., 2012; RIFM, 2000a; RIFM, 2013; Singal et al., 2014.

Literature Search and Risk Assessment Completed on: 05/06/2014.

10.1.4. Skin sensitization

Based on existing material specific data and read across to methyl dihydrojasmonate (CAS # 24851-98-7), methyl hexyl oxo cyclopentanone carboxylate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on existing material specific data and read across to methyl dihydrojasmonate (CAS # 24851-98-7; See section 5), methyl hexyl oxo cyclopentanone carboxylate does not present a concern for skin sensitization. Methyl dihydrojasmonate and methyl hexyl oxo cyclopentanone carboxylate are not predicted to react with skin proteins (Toxtree 2.5.0; OECD toolbox v3.3; Natsch et al., 2007; Natsch and Gfeller, 2008). No animal studies are available for methyl hexyl oxo cyclopentanone carboxylate. In a guinea pig maximization test, performed at the highest maximized concentrations of the available guinea pig studies for read across material methyl dihydrojasmonate, no sensitization reactions were observed (ECHA Dossier, accessed 05/05/2014). In a Buehler test conducted in guinea pigs and the Local Lymph Node Assay (LLNA), methyl dihydrojasmonate was reported to be negative up to the maximum concentration tested of 10% and 40%, respectively in each assay (ECHA Dossier, accessed 05/05/2014; RIFM, 1971a; RIFM, 2004a). In a human maximization test, no reactions were observed to 2% (1386 μg/cm^2) methyl hexyl oxo cyclopentanone carboxylate (RIFM, 1972). Additionally, in Human Repeated Insult Patch Tests no reactions indicative of sensitization were observed at the maximum reported test concentration of 20% (10,000 μg/cm^2) and in a human maximization test at 20% (13,800 μg/cm^2) (RIFM, 2003b; RIFM, 2005; RIFM, 1971b; RIFM, 1971c; RIFM, 1976).

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/27/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, methyl hexyl oxo cyclopentanone carboxylate 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 methyl hexyl oxo cyclopentanone carboxylate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern (1000 L mol^{-1} cm^{-1}) for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, methyl hexyl oxo cyclopentanone carboxylate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/20/2016.

10.1.6. Local respiratory toxicity

There are no inhalation data available on methyl hexyl oxo cyclopentanone carboxylate; however, in an acute, two week inhalation study for the analog methyl dihydrojasmonate (CAS # 24851-98-7; see section 5), a NOEC of 93 mg/m^3 was reported by RIFM, 2013.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2 week, acute inhalation study conducted in rats a NOEC of 93 mg/m^3 (the highest concentration tested) was reported for methyl dihydrojasmonate (RIFM, 2013). This test substance was tolerated at all exposure levels with no significant change in bronchoalveolar lavage cell types, protein levels, inflammatory cytokines, body or organ weight, and no histological changes indicative of inflammation were observed in the lung or nose.

This NOEC expressed in mg/kg lung weight/day is:

- (93 mg/m3) (1m3/1000 L) = 0.093 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.093 mg/L) (61.2 L/d) = 5.7 mg/day
- (5.7 mg/day)/(0.0016 kg lung weight of rat*) = 3562.5 mg/kg lung weight/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 2.34%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.22 mg/day—as calculated using RIFM's 2-Box/MPPD *in silico* models, and based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics. To compare this estimated exposure with the NOEC reported by Randazzo, and expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.34 mg/kg lung weight/day resulting in a MOE of 10478 (i.e., [3562.5 mg/kg lung weight/day]/[0.34 mg/kg lung weight/day]).

The MOE is greater than 100. Without the adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 2.34% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

Additional References: Isola et al., 2003b; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003c; Isola et al., 2003a; Isola et al., 2004b; Smith et al., 2004; RIFM, 2004b; Rogers et al., 2005; Singal et al., 2014; Isola et al., 2004a.

Literature Search and Risk Assessment Completed on: 05/26/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of methyl hexyl oxo cyclopentanone carboxylate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or

PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, methyl hexyl oxo cyclopentanone carboxylate 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 EPISUITE ver 4.1 did not identify methyl hexyl oxo cyclopentanone carboxylate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), methyl hexyl oxo cyclopentanone carboxylate presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1996: The biodegradability of the test material was tested in the Two Phase Closed Bottle Test/BODIS-Test (BOD Test for insoluble substances) according to the OECD 301D method. The method represents a modification of the Closed Bottle Test. At a test concentration of 100 mg ThOD/lh biodegradation of 86% ThoD/COD was achieved within the 28-day test period.

RIFM, 2002: Biodegradability was determined by a modified CO_2-Evolution Test (Modified Sturm Test) according to the OECD 301B method. Methyl hexyl oxo cyclopentanone carboxylate (29 mg/L) was added to glass bottles containing test medium inoculated with activated sludge. The maximum mean degradation was 73.1% after 28 days.

10.2.3.2. Ecotoxicity. RIFM, 2008a: A 72 h algae acute toxicity test study was conducted according to the OECD 201 method. Under the conditions of the study, the EC50 for growth rate reduction was 12 mg/L and the EC50 for yield inhibition was 3.5 mg/L. The NOEC for both growth rate reduction and yield inhibition was 1.0 mg/L.

10.2.3.3. Other available data. Methyl hexyl oxo cyclopentanone carboxylate has been pre-registered for REACH with no additional data at this time.

11. Risk assessment refinement

Since methyl hexyl oxo cyclopentanone carboxylate has passed the screening criteria, measured data is included in the 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	42.86 mg/L			1,000,000	0.04286 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	8.155 mg/L	15.27 mg/L	5.569 mg/L	10,000	0.5569 μg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	24.75 mg/L	15.38 mg/L	16.62 mg/L			Neutral Organics SAR (baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.98	2.98
Biodegradation Factor Used	1	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 additional assessment is necessary.

The RIFM PNEC is 0.5569 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 05/07/2014.

12. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
  - **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  - **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
  - **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

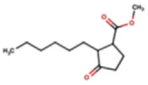
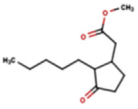
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.028.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.028.

Appendix

	Target Material	Read across Material
Principal Name	Methyl hexyl oxo cyclopentanone carboxylate	Methyl dihydrojasmonate
CAS No.	37172-53-5	24851-98-7
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/37172-53-5.html	http://www.thegoodscentscompany.com/opl/24851-98-7.html
Read-across endpoint		•Genotoxicity •Repeated Dose •Devel/Repro •Skin sensitization •Respiratory
Molecular Formula	C13H22O3	C13H22O3
Molecular Weight	226.32	226.32
Melting Point (°C, EPISUITE)	73.64	73.64
Boiling Point (°C, EPISUITE)	309.32	309.32
Vapor Pressure(Pa @ 25°C, EPISUITE)	0.05493	0.1587
Log K_{ow} (KOWWIN v1.68 in EPI SUITE)	2.98	2.98
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	91.72	91.72
J_{max} (mg/cm^2/h, SAM)	12.58071299	13.94093406
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	0.050845	0.050845
Similarity (Tanimoto score)[1]		82%
Skin Absorption		
Skin Absorption Percentage (SAM)	80%	80%
Genotoxicity		
DNA binding (OASIS v1.1)	•No alert found	•No alert found
DNA binding (OECD)	•No alert found	•No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found	•No alert found
DNA alerts for Ames, MN, CA (OASIS v1.1)	•No alert found	•No alert found
In vitro mutagenicity (Ames test) alerts (ISS)	•No alert found	•No alert found
In vivo mutagenicity (Micronucleus) alerts (ISS)	•H-acceptor-path3-H-acceptor	•H-acceptor-path3-H-acceptor

(*continued on next page*)

(*continued*)

	Target Material	Read across Material
Oncologic classification (OECD)	•Not classified	•Not classified
Repeated Dose Toxicity		
Repeated dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (moderate reliability)	Toxicant (moderate reliability)
Skin Sensitization		
Protein binding (OASIS v1.1)	•No alert found	•No alert found
Protein binding (OECD)	•No alert found	•No alert found
Protein binding potency (OECD)	•Not possible to classify according to these rules (GSH)	•Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization (OASIS v1.1)	•No alert found	•No alert found
Skin sensitization model (CAESAR v2.1.6)	Sensitizer (good reliability)	Sensitizer (good reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See Supplemental Data 1	See Supplemental 2

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Abstract

There are insufficient toxicity data on methyl hexyl oxo cyclopentanone carboxylate (RIFM# 1168, CAS# 37172-53-5). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012).

Conclusion/rationale

- Methyl dihydrojasmonate (analog) was used as a read-across for methyl hexyl oxo cyclopentanone carboxylate (target) based on:
  - o The target and analog belong to the generic class of aliphatic esters, specifically, ketone/cyclopentanones & cyclopentenones/cyclopentanones/keto esters.
  - o The target and analog have the samilar carboxylic acid part and same alcohol part.
  - o The key differences are that the target has a longer alkyl chain and shorter carboxylic acid chain than the analog. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, their toxicology profiles are expected to be similar.
  - o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o The target and analog show similar alerts for protein binding.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.

Explanation of Cramer class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1.Normal constituent of the body? No
Q2.Contains functional groups associated with enhanced toxicity? No
Q3.Contains elements other than C, H, O, N, divalent S? No
Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6.Benzene derivative with certain substituents? No
Q7.Heterocyclic? No
Q16.Common terpene? No
Q17.Readily hydrolyzed to a common terpene? No
Q19.Open chain? No
Q23.Aromatic? No
Q24.Monocarbocyclic with simple substituents? No
Q25. Cyclopropane, cyclobutane with substituents in Q24 or a mono or bicyclic sulphide or mercaptan? No
Q26.Monocycloalkanone or a bicyclocompound? Yes - Class Intermediate (Class II).

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