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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, Methyl jasmonate, CAS Registry Number 1211-29-6

A.M. Api [a, *], D. Belsito [b], S. Bhatia [a], D. Botelho [a], D. Browne [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], P. Calow [f], M.L. Dagli [g], M. Date [a], W. Dekant [h], C. Deodhar [a], A.D. Fryer [i], K. Joshi [a], L. Kromidas [a], S. La Cava [a], J.F. Lalko [a], A. Lapczynski [a], D.C. Liebler [j], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [k], V.T. Politano [a], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [l], J. Shen [a], I.G. Sipes [m], Y. Thakkar [a], S. Tsang [a], J. Wahler [a], B. Wall [a], D.K. Wilcox [a]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
[b] Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA
[c] Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE 20502, Sweden
[d] Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA
[e] Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany
[f] Member RIFM Expert Panel, Humphrey School of Public Affairs, University of Minnesota, 301 19th Avenue South, Minneapolis, MN 55455, USA
[g] Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo CEP 05508-900, Brazil
[h] Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany
[i] Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA
[j] Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, USA
[k] Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA 19104-3083, USA
[l] Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA
[m] Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA

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* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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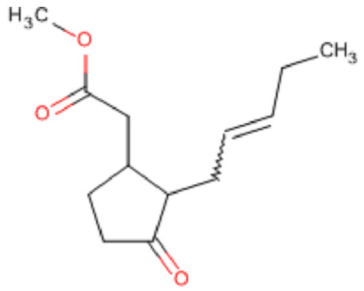
1. Identification

Version: 112816. This version replaces any previous versions.
Name: Methyl jasmonate
CAS Registry Number: 1211-29-6



Additional CAS Numbers*:
39924-52-2 Methyl 3-oxo-2-(pent-2-enyl)cyclopentaneacetate
*This material was included in this assessment because they are a mixture of isomers.

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

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 and data on the target material. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2000a,b,c,d; RIFM, 1998)

(*continued on next page*)

(*continued*)

Repeated Dose Toxicity: NOEL = 100 mg/kg/day	(RIFM, 2000a,b,c,d)
Developmental and Reproductive Toxicity: NOAEL = 120 mg/kg/day and 300 mg/kg/day respectively (Politano et al., 2008; JECDB, 2012)	
Skin Sensitization: Not sensitizing (ECHA Dossier, accessed 05/05/2014; RIFM, 1971a; RIFM, 2003a; RIFM, 2004b; RIFM, 2005; RIFM, 1971b; RIFM, 1978a,b; RIFM, 1976)	
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1980a,b,c)	
Local Respiratory Toxicity: NOEC = 93 mg/m^3 (RIFM, 2013b)	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening Level: 3.1196	(EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 30.76 L/kg	(EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 66.01 mg/L	(Salvito et al., 2002)
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: Fish LC50: 66.01 mg/L	(Salvito et al., 2002)
RIFM PNEC is: 0.066 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at screening level	

2. Physical data**

Chemical Name: Methyl jasmonate	Chemical Name: Methyl 3-oxo-2-(pent-2-enyl)cyclopentaneacetate
CAS Registry Number: 1211-29-6	**CAS Registry Number:** 39924-52-2
Synonyms: Cyclopentaneacetic acid, 3-oxo-2-(2-pentenyl)-, methyl ester (1R,2bZ); Methyl jasmonate; Methyl 3-oxo-2-(2-pentenyl)cyclopentyl acetate; Methyl (1R-(1a,2b(Z)))-3-oxo-2-(pent-2-enyl)cyclopentaneacetate; Methyl (2-pent-2-enyl-3-oxo-1-cyclopentyl) acetate; ﾒﾁﾙ＝［３－ｵｷｿ－２－（２－ﾍﾟﾝﾃﾆﾙ）ｼｸﾛﾍﾟﾝﾁﾙ］ｱｾﾀｰﾄ; Methyl (3-oxo-2-pent-2-en-1-ylcyclopentyl)acetate	**Synonyms:** Cyclopentaneacetic acid, 3-oxo-2-(2-pentenyl)-, methyl ester (isomer unspecified); Methyl (3-oxo-2-pent-2-en-1-ylcyclopentyl)acetate; Methyl 2-pentenyl-3-oxocyclopentaneacetate; 2-〔3-ｵｷｿｰ2-(ﾍﾟﾝﾀｰ2-ｴﾝｰ1-ｲﾙ)ｼｸﾛﾍﾟﾝﾁﾙ］ｱｾﾀｰﾄ
Molecular Formula: $C_{13}H_{20}O_3$	**Molecular Formula:** $C_{13}H_{20}O_3$
Molecular Weight: 224.3	**Molecular Weight:** 224.0
RIFM Number: 5062	**RIFM Number:** 5695

1. **Boiling Point:** >300 °C [FMA database], 313.62 °C [EPI Suite]
2. **Flash Point:** >200°F; CC [FMA database]
3. **Log K_{OW}:** 2.76 [EPI Suite]
4. **Melting Point**: 72.35 °C [EPI Suite]
5. **Water Solubility:** 143.5 mg/L [EPI Suite]
6. Specific Gravity: 1.02 [FMA database]
7. **Vapor Pressure:** 0.000176 mm Hg @ 20 °C [EPI Suite 4.0], 0.000337 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 clear oily liquid with a medium floral, fresh, petal, magnolia, oily, and waxy odor. It is also described as sweet, fruity, waxy, floral and green. The taste at 15 ppm was described as floral, fruity, green, waxy, seedy and melon-like * *http://www.thegoodscentscompany.com/data/rw1000141.html, retrieved 07/16/14

**Physical data are identical for both materials in this assessment.

3. Exposure***

1. **Volume of Use (worldwide band):** <1 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 0.12% (IFRA, 2008)
3. **97.5th Percentile:** 0.25% (IFRA, 2008)
4. **Dermal Exposure*:** 0.0063 mg/kg/day (IFRA, 2008)
5. **Oral Exposure:** Not available
6. **Inhalation Exposures**:** 0.00039 mg/kg/day or 0.023 mg/day (IFRA, 2008)
7. **Total Systemic Exposure (Dermal + Inhalation):** 0.0016 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.

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 97.5th Percentile, average maximum concentration in hydroalcoholics, inhalation exposure and total exposure.

4. Derivation of systemic absorption

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

RIFM, 2001c (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. A full-thickness human female breast and abdominal skin, obtained from cosmetic surgery and stored at −20 °C was thawed for processing. The epidermis was gently removed from the dermis and discarded, the remaining epidermal membrane floated onto the surface of water and taken up onto the aluminum foil, then thoroughly dried and stored flat at −20 °C until used. 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 = 0.0016 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 jasmonate is reported to occur in the following foods* and in some natural complex substances (NCS):

Wormwood oil (Artemisia absinthium L.)

Methyl 3-oxo-2-(pent-2-enyl)cyclopentaneacetate is reported to occur in the following foods*:

Citrus fruits.

Mentha oils Tea*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

Methyl jasmonate is pre-Registered for 2010; No dossier available as of 11/28/2016. Methyl 3-oxo-2-(pent-2-enyl)cyclopentaneacetate is 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 jasmonate does not present a concern for genotoxicity.

10.1.2. Risk assessment

Methyl jasmonate was tested in the BlueScreen assay and was found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern for gentotoxicity (RIFM, 2013a). There are no studies assessing the mutagenic activity of methyl jasmonate however, the material methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) was identified as sufficient to use as read across. The mutagenic activity of methyl dihydrojasmonate 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. *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 uvrA were treated with methyl dihydrojasmonate in DMSO (dimethyl sulfoxide) at concentrations of 100, 333, 1000, 3333 and 5000 μg/ml in the presence and absence of metabolically active microsomal fraction (S9 mix). No significant increase in the number of revertant colonies was observed in the tester strains at any concentration (RIFM, 2000a,b,c,d). Under the conditions of the study, methyl dihydrojasmonate was considered negative in the Ames test.

There are no studies assessing the clastogenic potential of methyl jasmonate however, the material methyl dihydrojasmonate (CAS # 2481-98-7; 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 considered not clastogenic in the *in vivo* micronucleus test. Additionally, the RIFM 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 genotoxic potential (Belsito et al., 2012).

Based on the available data, methyl dihydrojasmonate does not present a concern for genotoxic potential, this can be applied to methyl jasmonate.

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

Literature Search and Risk Assessment Completed on: 05/09/14.

10.1.3. Repeated dose toxicity

The margin of exposure for methyl jasmonate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on methyl jasmonate. 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. Methyl dihydrojasmonate was administered in the diet of Sprague-Dawley rats (10/sex/group) at doses of 0, 10, 50 or 100 mg/kg/day for 3 months. The NOEL was determined to be 100 mg/kg/day, the highest dosage tested (RIFM, 2000a,b,c,d). A dermal absorption study conducted on human skin on read across material, methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) resulted in a 45.9% skin absorption value (RIFM, 2001c; see section 4). **Therefore, the methyl jasmonate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl dihydrojasmonate NOEL in mg/kg/day divided by the total systemic exposure for methyl jasmonate, 100/0.0016 or 62500.**

In addition, the total systemic exposure for methyl jasmonate (1.6 μg/kg bw/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

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

Literature Search and Risk Assessment Completed on: 05/06/14.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for methyl jasmonate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on methyl jasmonate. Read across material methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) has a gavage developmental toxicity study in rats. Methyl dihydrojasmonate was evaluated for developmental toxicity in presumed pregnant Sprague-Dawley rats (25/group) at oral dosages of 0, 40, 80 or 120 mg/kg/day in corn oil administered on gestational days 7–20. The NOAEL for developmental toxicity was determined to be 120 mg/kg/day, the highest dosage tested (Politano et al., 2008; data also available in RIFM, 2007; Bhatia et al., 2008). A dermal absorption study conducted on human skin on read across material, methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) resulted in a 45.9% skin absorption value (RIFM, 2001c; see section 4). **Therefore, the methyl jasmonate MOE for the developmental toxicity endpoint can be calculated by dividing the methyl dihydrojasmonate NOAEL in mg/kg/day by the total systemic exposure for methyl jasmonate, 120/0.0016 or 75000.**

There are no reproductive toxicity data on methyl jasmonate. 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 Sprague-Dawley rats. Groups of 12 male rats/dose were administered 0, 100, 300, or 1000 mg/kg/day methyl dihydrojasmonate for 42 days; on day 43 of study, 7, 12, 12, and 7 rats from the 0, 100, 300, or 1000 mg/kg/day groups, respectively, were euthanized. The remaining 5 male rats/dose at 0 and 1000 mg/kg/day were observed following a 14-day treatment-free recovery period. Groups of 12 female rats were administered 0, 100, 300, or 1000 mg/kg/day methyl dihydrojasmonate for a 15 day premating period, through gestation, and 4 days of lactation, and euthanized on day 5 of lactation. Satellite groups of 10 female rats/dose were administered 0 or 1000 mg/kg/day methyl dihydrojasmonate for 42 days; on day 43 of study, 5 female rats/dose were euthanized. The remaining 5 female rats/dose at 0 and 1000 mg/kg/day were observed following a 14-day treatment-free recovery period. The NOAELs for reproductive toxicity were determined to be 1000 mg/kg/day in males, the highest dosage tested, and 300 mg/kg/day in females, based on decreased gestational bodyweight gain and decreased pup bodyweights on day 0 (JECDB, 2012). A dermal absorption study conducted on human skin on read across material, methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5) resulted in a 45.9% skin absorption value (RIFM, 2001c; see section 4). **Therefore, the methyl jasmonate MOE for the reproductive toxicity endpoint can be calculated by dividing the methyl dihydrojasmonate NOAEL in mg/kg/day by the total systemic exposure for methyl jasmonate, 300/0.0016 or 187500.**

In addition, the total systemic exposure for methyl jasmonate (1.6 μg/kg bw/day) is below the TTC (9 μg/kg bw/day) for the developmental and reproductive toxicity endpoints at the current level of use.

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

Literature Search and Risk Assessment Completed on: 06/13/16.

10.1.7. Skin sensitization

Dihydrojasmonate (CAS # 24851-98-7); methyl jasmonate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on existing material specific data and read across to methyl dihydrojasmonate (CAS # 24851-98-7; see Section 5), methyl jasmonate does not present a concern for skin sensitization. Methyl dihydrojasmonate and methyl jasmonate are not predicted to react with skin proteins and would not be expected to act as skin sensitizers (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.3; Natsch et al., 2007, Natsch & Gfeller, 2008). In a Buehler sensitization study, no reactions were observed with 10% methyl jasmonate in alcohol SDA 39C (RIFM, 1980a). Similarly, in a modified 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, 2004b; RIFM, 1980a). In a guinea pig

maximization test, performed at the highest maximized concentrations of the available guinea pig studies on read across material methyl dihydrojasmonate, no sensitization reactions were observed (ECHA Dossier, accessed 05/05/2014). In Human Repeated Insult Patch Tests no reactions indicative of sensitization were observed to either methyl dihydrojasmonate up to 10,000 μg/cm² or methyl jasmonate up to 1000 μg/cm² in ethanol based vehicle (RIFM, 1980b; RIFM, 2003a; RIFM, 2005; RIFM, 1971b; RIFM, 1978a,b; RIFM, 1976). In a human maximization test, no reactions were observed to 13,800 μg/cm^2 methyl dihydrojasmonate in petrolatum (RIFM, 1971c).

Additional References: RIFM, 1981; RIFM, 1982; RIFM, 1986; RIFM, 1988.

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

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and data from a human study, methyl jasmonate does not present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

UV/Vis absorption spectra for methyl jasmonate indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L · mol^{-1} · cm^{-1} (Henry et al., 2009). In a phototoxicity and photoallergenicity study conducted in human volunteers, topical application of 10% methyl jasmonate followed by irradiation with UV, did not result in any phototoxic or photoallergenic skin reactions (RIFM, 1980a,b,c). Based on lack of absorbance in the critical range and data from the human study, methyl jasmonate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/31/16.

10.1.11. Local Respiratory Toxicity

There are no inhalation data available on methyl jasmonate; 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, 2013b.

10.1.12. 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 two week, acute inhalation study conducted in rats a NOEC of 93 mg/m^3 (the highest concentration tested) was reported for methyl dihydrojasmonate (RIFM, 2013b). 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/m^3) (1m^3/1000 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 0.25%. 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 0.023 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, 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 0.035 mg/kg lung weight/day resulting in a MOE of 101786 (i.e., [3562.5 mg/kg lung weight/day]/[0.035 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 0.25% 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, 2nd 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., 2003a; Rogers et al., 2003; RIFM, 2003c; RIFM, 2003b; Isola et al., 2003b; Isola et al., 2004a, 2004b; Smith et al., 2004; RIFM, 2004a; Rogers et al., 2005; Singal et al., 2014.

Literature Search and Risk Assessment Completed on: 5/26/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of methyl jasmonate 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 K_{ow} 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 jasmonate was identified as a fragrance material with no 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 jasmonate 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).

10.2.2. Risk assessment

Based on current Volume of use (2011), methyl jasmonate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. Methyl jasmonate has been pre-registered for REACH with no additional data at this time.

10.2.3.4. Risk assessment refinement. 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)**	66.01 mg/L			1,000,000	0.066 μg/L	

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.76	2.76
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1*	<1*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Regional Volumes for CAS# 1211-29-6 and CAS# 39924-52-2 have been added.

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

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

The RIFM PNEC is 0.066 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable, cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 5/07/14.

11. 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.

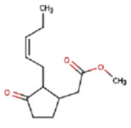
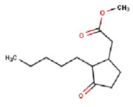
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.03.035.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.035.

Appendix

	Target Material	Read across Material
Principal Name	Methyl jasmonate	Methyl dihydrojasmonate
CAS No.	1211-29-6	24851-98-7
Structure		
3D Structure		

(*continued*)

	Target Material	Read across Material
	http://www.thegoodscentscompany.com/opl/1211-29-6.html	http://www.thegoodscentscompany.com/opl/24851-98-7.html
Read-across endpoint		• Genotoxicity • Repeated Dose • Devel/Repro • Skin sensitization • Respiratory
Molecular Formula	C13H20O3	C13H22O3
Molecular Weight	224.3	226.32
Melting Point (°C, EPISUITE)	72.35	73.64
Boiling Point (°C, EPISUITE)	313.62	309.32
Vapor Pressure (Pa @ 25°C, EPISUITE) Log K_{ow} (KOWWIN v1.68 in EPISUITE)	0.04493 2.76	0.1587 2.98
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	143.5	91.72
J_{max} (mg/cm^2/h, SAM)	10.89502246	13.94093406
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	0.044725	0.050845
Similarity (Tanimoto score)[a]		71%
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
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)	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 Data 2

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

Summary

There are insufficient toxicity data on methyl jasmonate (RIFM# 5062, CAS# 1211-29-6). 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 jasmonate (target) based on:
  - The target and analog belong to the generic class of aliphatic esters, specifically, ketone/cyclopentanones & cyclopentenones/cyclopentanones/keto esters.
  - The target and analog have the similar carboxylic acid part and same alcohol part.
  - The only difference is that the double bond in the alkyl chain of the target has been saturated in the analog. The difference between structures does not essentially change the

physicochemical properties nor raise any additional structural alerts and therefore, their toxicity profiles are expected to be similar.

- The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
- 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.
- The target and analog show similar alerts for protein binding.
- 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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