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Short Review

RIFM fragrance ingredient safety assessment, methyl dihydrojasmonate, CAS registry number 24851-98-7

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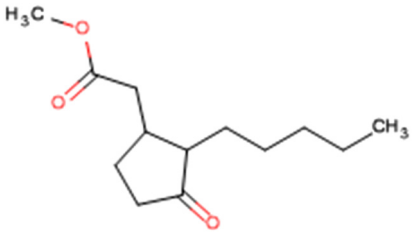

Abbreviation/Definition list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 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
DEREK – Derek nexus is an *in silico* tool used to identify structural alerts

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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 RIFM's Criteria Document (Api et al., 2014) and 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 endpoint 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 composed of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as environmental assessment. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 100 mg/kg/day, based on an OECD 408 dietary 90-day subchronic toxicity study conducted in rats that resulted in an MOE of 256, considering 45.9% absorption from skin contact and 100% from inhalation. An MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not Genotoxic (RIFM, 2000; RIFM, 2001; RIFM, 1998; RIFM, 2001a)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day (RIFM, 2000a)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day (JECDB:Methyl(2-pentyl-3oxocyclopentyl)acetate)
Skin Sensitization: Not sensitizing (ECHA Dossier, accessed 03/25/2013; RIFM, 1971; RIFM, 2004)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (Belsito et al., 2012)
Local Respiratory Toxicity: NOAEC = 10 ppm or 93 mg/m^3 (0.093 mg/L) (RIFM, 2013)

Environmental Safety Assessment
Hazard Assessment:Persistence: Critical Measured Value: PEC/PNEC (North America and Europe) >1 (Salvito et al., 2002)
Bioaccumulation: Screening Level: 42.65 L/kg (EPISUITE ver 4.1, 2000–2011)
Ecotoxicity: Critical Ecotoxicity Endpoint**:** 21 d *Daphnia* NOEC: 0.79 mg/L (RIFM, 2000b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 21 d *Daphnia* NOEC: 0.79 mg/L (RIFM, 2000b)
RIFM PNEC is: 15.8 µg/L
- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Methyl dihydrojasmonate
2. **CAS Registry Number:** 24851-98-7
3. **Synonyms:** Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester, Hedione, Methyl dihydrojasmonate, Methyl 3-oxo-2-pentylcyclopentaneacetate, Methyl (2-pentyl-3-oxocyclopentyl)acetate, 3-Oxo-2-pentylcyclopentaneacetic acid, methyl ester, Dihyrojasmonic acid methyl ester, 2-Amylcyclopentanoneacetic acid, methyl ester, Methyl (2-amyl-3-oxocyclopentyl)acetate, Methyldihydrojasmonate, Methydihydro-Jasmonate, メチル （2-ﾍﾟﾝﾁﾙ-3-ｵｷｿ-ｼｸﾛﾍﾟﾝﾁﾙ） ｱｾﾃｰﾄ, Methyl (3-oxo-2-pentylcyclopentyl)acetate, Jasmodione, Paradisone
4. **Molecular Formula:** $C_{13}H_{22}O_3$
5. **Molecular Weight:** 226.32
6. **RIFM Number:** 850

2. Physical data

1. **Boiling Point:** 309.32 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (IFRA)
3. **Log K_{ow}:** 3.1 at 35 °C [RIFM, 1997], 2.98 (EPI Suite)
4. **Melting Point:** 73.64 °C (EPI Suite)
5. **Water Solubility:** 91.72 mg/L (EPI Suite)
6. **Specific Gravity:** 0.999 g/ml [RIFM, 1994b], 0.998–1.006 @ 20/20 °C (RIFM), 0.998 (IFRA)

7. **Vapor Pressure:** 0.000713 mm Hg @ 20 °C (EPI Suite 4.0), 0.00119 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm
9. **Appearance/Organoleptic:** A pale yellowish or almost colorless oily liquid with a powerful but warm, sweet-floral, jasmine-like and fruity odor (Arctander, 1969)

3. Exposure

1. **Volume of Use (worldwide band):** >1000 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 15.16% (IFRA, 2002)
3. **97.5th Percentile:** 27.95% (IFRA, 2002)
4. **Dermal Exposure*:** 0.7122 mg/kg/day (IFRA, 2002)
5. **Oral Exposure:** Not available
6. **Inhalation Exposures**:** 0.043 mg/kg/day (IFRA, 2002)
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.7122 mg/kg/day × 45.9% absorption) + 0.061 mg/kg/day = 0.39 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., antiperspirant, 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.

4. Derivation of systemic absorption

1. **Dermal:** 45.9%

RIFM (2001b); (data also available in Isola and Api, 2002): An *in vitro* human percutaneous absorption study was designed to determine the *in vitro* skin penetration rate and distribution of the radiolabeled material (C^{14}-labeled) methyl dihydrojasmonate, 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 hours 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 hour period was assessed using PTFE sheets mounted in the diffusion cells. The PTFE sheets were removed at 1, 2, 4, 8, 24, and 48 hours after dosing and washed with solvent. After 24 and 36 hours, the receptor phase level of methyl dihydrojasmonate was 30.79% and 40.12% of applied dose, respectively. Following 48 hours 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 hours 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 = (0.7122 mg/kg/day × 45.9%) + 0.061 mg/kg/day = 0.39 mg/kg/day

5. Computational toxicology evaluation

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

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

* See Appendix below for explanation.

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

6. Metabolism

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

7. Natural Occurrence (discrete chemical) or Composition (NCS)

Methyl dihydrojasmonate is reported to occur in food*:

Black tea
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

Available; accessed on 05/08/13: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9e9c5412-47b8-2b52-e044-00144f67d031/DISS-9e9c5412-47b8-2b52-e044-00144f67d031_DISS-9e9c5412-47b8-2b52-e044-00144f67d031.html

10. Summary

1. Human Health Endpoint Summaries:

10.1. Genotoxicity

Based on the current existing data and use levels, methyl dihydrojasmonate does not present a concern for genetic toxicity.

10.1.1. Risk assessment

The genotoxic potential of methyl dihydrojasmonate was evaluated by mutagenicity in bacteria and in cultured mouse L5718Y tk+/– cells, and cytogenetics *in vivo*. Methyl dihydrojasmonate was shown to be non-mutagenic in an Ames assay, following OECD TG 471, conducted in five *S. typhimurium* strains up to 5000 µg/plate both with and without

metabolic activation. Additionally, data from several mouse lymphoma assays (MLA) are available. While one MLA demonstrated positive effects when tested up to 300 μg/ml, both with and without metabolic activation (RIFM, 1979), a more recent MLA, following OECD TG 767, demonstrated negative effects both with and without metabolic activation, when tested up to 325 μg/ml (RIFM, 2001). With regard to clastogenicity, a mouse micronucleus test following OECD TG 474, was conducted in IRC mice. The mice received an IP injection of methyl dihydrojasmonate up to 1120 mg/kg. Methyl dihydrojasmonate was found to be non-clastogenic (RIFM, 1998). Further evidence indicating that methyl dihydrojasmonate is not genotoxic comes from an *in vivo* unscheduled DNA synthesis test, conducted following OECD TG 486 (RIFM, 2001a).

The genotoxicity testing battery is complete, and indicates that methyl dihydrojasmonate is neither mutagenic nor clastogenic. Additionally, RIFM's Expert Panel and Adjunct Reproduction Advisory Group* after reviewing the Structure Activity Relation category, Ketone/Cyclopentanones & Cyclopentenones/Cyclopentanones/Keto Esters, of which methyl dihydrojasmonate is a member, concluded that they do not have genotoxic potential (Belsito et al., 2012).

* RIFM's Expert Panel and Adjunct Reproduction Advisory Group are composed of an independent panel of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 2000c; RIFM, 1978; RIFM, 1979; RIFM, 1987

Literature Search and Risk Assessment Completed on: 03/25/13

10.2. Repeated dose toxicity

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

10.2.1. Risk assessment

The repeated dose toxicity data on methyl dihydrojasmonate are sufficient for the repeated dose toxicity endpoint. An OECD 408 dietary 90-day subchronic toxicity study was conducted in rats. The NOAEL was determined to be 100 mg/kg/day, the highest dosage tested (RIFM, 2000a). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.39 or 256.

Additional References: RIFM, 2000d; RIFM, 2013; Hall et al., 1974; Belsito et al., 2012; Scognamiglio et al., 2012; Singal et al., 2014

Literature Search and Risk Assessment Completed on: 05/07/14

10.3. Developmental and reproductive toxicity

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

10.3.1. Risk assessment

The developmental toxicity data on methyl dihydrojasmonate are sufficient for the developmental toxicity endpoint. In a gavage developmental toxicity study conducted in rats the NOAEL for developmental toxicity was determined to be 120 mg/kg/day, the highest dosage tested (Politano et al., 2008). Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 120/0.39 or 308.

The reproductive toxicity data on methyl dihydrojasmonate are sufficient for the reproductive toxicity endpoint. An OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in rats. The NOAEL for reproductive toxicity was 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: Methyl (2-pentyl-3-oxocyclopentyl)acetate). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.39 or 769.

Additional References: RIFM, 2000d; RIFM, 2013; Hall et al., 1974; Belsito et al., 2012; Scognamiglio et al., 2012; Singal et al., 2014

Literature Search and Risk Assessment Completed on: 05/07/14

10.4. Skin sensitization

Based on the available data, methyl dihydrojasmonate does not present a concern for skin sensitization.

10.4.1. Risk assessment

Methyl dihydrojasmonate is not predicted to react with skin proteins (Toxtree 2.5.0; OECD toolbox v3.0; Natsch et al., 2007; Natsch and Gfeller, 2008). In a well-conducted guinea pig maximization test, performed at the highest maximized concentrations of the available guinea pig studies, no sensitization reactions were observed (ECHA Dossier, accessed 03/25/2013). 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 03/25/2013; RIFM, 1971; RIFM, 2004). 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, 2003; RIFM, 2005; RIFM, 1971a; RIFM, 1971b; RIFM, 1976). Based on the available data, methyl dihydrojasmonate does not present a concern for skin sensitization.

Additional References: RIFM, 1979a; RIFM, 1980; RIFM, 1977; RIFM, 1981; RIFM, 1981a; RIFM, 1981b; RIFM, 1982, RIFM, 1982a; RIFM, 1982b; RIFM, 1986

Literature Search and Risk Assessment Completed on: 03/25/13

10.5. Phototoxicity/photoallergenicity

Based on the existing data, methyl dihydrojasmonate does not present a concern for phototoxicity/photoallergenicity.

10.5.1. Risk assessment

RIFM's Expert Panel* reviewed the available phototoxicity data for methyl dihydrojasmonate, as part of an overall assessment of cyclopentanones/cyclopentenones, and concluded that the material does not present a concern for phototoxicity/photoallergenicity (Belsito et al., 2012). Methyl dihydrojasmonate does not significantly absorb in the UV range of 290–700 nm (molar absorption coefficient <1000) and therefore does not present a significant potential to be photoactivated. Additionally, the existing in vivo (guinea pigs and rats) data as reported by RIFM (1979b), RIFM (1979c), RIFM (1979d), RIFM (1986a), RIFM (1986b), RIFM (1979e), RIFM (1979f) and RIFM (1979) demonstrate, by a weight of evidence, that methyl dihydrojasmonate does not present a concern for phototoxicity/photoallergenicity.

* RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is composed of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Additional References: None

Literature Search and Risk Assessment Completed on: 03/25/13

10.6. Local respiratory toxicity

The margin of exposure for methyl dihydrojasmonate is adequate for the respiratory endpoint at the current level of use.

10.6.1. 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 an acute 2 week study done in rats, a NOAEC of 10 ppm (93 mg/m^3; the highest dose tested) was determined (RIFM, 2013) for methyl dihydrojasmonate. This substance was tolerated at all exposure levels up to 10 ppm (93 mg/m^3) with no significant change in bronchoalveolar lavage cell types, protein levels, or inflammatory cytokines measured. Furthermore, no histologic changes indicative of inflammation were observed in the lung or nose.

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

- (93 mg/m^3) (1m^3/1000L) = 0.093 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 minutes per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.093 mg/L) (61.2 L/d) = 5.69 mg/d
- (5.69 mg/d)/(0.0016 kg lung weight of rat*) = 3556.25 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 27.95%. 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 2.6 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD *in silico* models. To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 4 mg/kg lung weight/day resulting in an MOE of >889 (i.e., [3556.25 mg/kg lw/day]/[4 mg/kg lung weight/day]).

Since the MOE is significantly greater than 100, without the adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure, by inhalation, at 27.95% 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. Foundtions 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., 2003; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003b; Isola et al., 2003a; Isola et al., 2004; Smith et al., 2004; RIFM, 2004a; Isola et al., 2004a; Rogers et al., 2005

Literature Search and Risk Assessment Completed on: 12/20/13

10.7. Environmental Endpoint Summary

10.7.1. Screening-level assessment

A screening level risk assessment of methyl dihydrojasmonate 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). Following the RIFM Environmental Framework, methyl dihydrojasmonate 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 dihydrojasmonate as either being possibly persistent nor bio-accumulative 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.

10.7.2. Risk assessment

Based on current VoU (2011), methyl dihydrojasmonate presents a risk to the aquatic compartment in the screening level assessment.

10.7.3. Biodegradation

The ready biodegradability of methyl dihydrojasmonate has been determined by the manometric respirometry test (OECD 301F). 100 mg of the test substance was incubated for 28 days. Methyl dihydrojasmonate reached 89% biodegradation. The biodegradation rate after the 10-day window (days 6–16) was 82% (RIFM, 1994a).

A 28 day seal vessel test according to the OECD 301B method was conducted with 10 mg/l methyl dihydrojasmonate. The biodegradation of methyl dihydrojasmonate was 66.5% (RIFM, 1996).

A biodegradation study was conducted following OECD 301B method. 10 mg/l of methyl dihydrojasmonate was incubated for 28 days. The biodegradation of test substance after 28 days was 78% (RIFM, 1995).

10.7.4. Ecotoxicity

As a part of the *Daphnia magna* Reproduction Test, a 48 hour acute test according to the OECD guideline 202 Part II was conducted. The 48 hour EC50 was greater than 16.1 mg/l (highest dose tested). There was 42.5% immobilization at this measured concentration (RIFM, 2000b).

A 21 day *Daphnia magna* Reproduction Test according to the OECD guidelines 211 under static renewal test conditions was conducted to determine the effect of methyl dihydrojasmonate on survival, reproduction, and growth. The NOEC and LOEC for reproduction were 0.79 mg/l and 1.73 mg/l, respectively. The NOEC and LOEC for survival were 1.73 and 3.72 mg/L. The NOEC for growth was 1.73 mg/ (RIFM, 2000b).

10.7.5. Other available data

This material has been registered under REACH. Three additional aquatic toxicity studies are reported. All data are from the ECHA Chemical Information Website accessed 13 March 2013.

A 96 hour fish (*Oryzias latipes*) acute study according to the OECD 203 method was reported with an LC50 of 19 mg/l. A *Daphnia magna* 48 hr EC50 of 8.25 mg/l was reported as a result of the study conducted according to the OECD 202 method. In addition, a 72 hour algae inhibition test according to the OECD 201 method was reported with EbC50 of 18.2 mg/L, ErC50 of 45 mg/L, NOEC (biomass) of 6.84 mg/L and NOEC (growth) of 11.7 mg/L.

The PNEC was calculated to be 15.8 μg/L using an assessment factor of 50.

10.7.6. 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) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	33.70			1,000,000	0.033707	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.893	12.373	4.554	10,000	0.4554	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	19.117	12.015	13.624			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	19.0					
Daphnia		8.25	0.79	50	15.8	
Algae		18.2	6.84			

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

Exposure	Europe	North America
Log K_{ow} used	3.1	
Biodegradation Factor Used	1	
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000	>1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 15.8 μg/L. The revised PEC/PNECs for EU and NA are <1 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: 03/25/13

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.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix

Explanation of Cramer class

The Cramer class of the target material was determined based on 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 hydrolysed to a common terpene **No**
Q19. Open chain **No**
Q23. Aromatic **No**
Q24. Monocarbocyclic with simple substituents **No**
Q25. Cyclopropane, etc. (see explanation in Cramer et al., 1978) **No**
Q26. Monocycloalkanone or a bicyclocompound **Yes** Class Intermediate (Class II)

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