Short Review

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

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ARTICLE INFO

Article history:
Received 19 November 2014
Accepted 13 January 2015
Available online

Version: 011414. This version replaces any previous versions.

Name: Methyl dihydrojasmonate

CAS Registry Number: 24851-98-7

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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http://dx.doi.org/10.1016/j.fct.2015.01.006
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Please cite this article in press as: A.M. Api, et al., RIFM fragrance ingredient safety assessment, methyl dihydrojasmonate, CAS registry number 24851-98-7, Food and Chemical Toxicology (2015), doi: 10.1016/j.fct.2015.01.006
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-pentylcyclopentanecarboxylic acid, methyl ester, Dihydrojasmonic acid, methyl ester, 2-Amylcyclopentanoneacetic acid, methyl ester, Methyl (2-amyl-3-oxocyclopentyl)acetate, Methyl dihydrojasmonate, Methyl dihydrojasmonate, Methyl dihydrojasmonate, Methyl dihydrojasmonate, Methyl dihydrojasmonate, Methyl dihydrojasmonate, Methyl (3-oxo-2-pentylcyclopentyl)acetate, Jasmodione, Paradisone

2. Physical data

1. Boiling Point: 309.32 °C (EPI Suite)

2. Flash Point: > 200 °F; CC (IFRA)

3. Log Kow: 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: 0.998 g/ml [RIFM, 1994b], 0.998-1.006 @ 20/20 °C (RIFM)

3. Molecular Formula: C13H22O3

5. Molecular Weight: 226.32

6. RIFM Number: 850

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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 x 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 (C14-labeled) methyl dihydrojasmonate, at 20 μl/cm² 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 taken at 2, 8, 24, 36, and 48 hours and were analyzed by liquid scintillation. 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 methyldihydrojasmonate was 45.9 ± 3.5% of the applied dose. 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/cm² and 20.2 ± 2.7 μg/cm², 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 x 45.9%) + 0.061 mg/kg/day = 0.39 mg/kg/day

5. **Computational toxicology evaluation**

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

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree v 2.6</th>
<th>OECD QSAR Toolbox v 3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>II*</td>
<td>II</td>
<td>III</td>
</tr>
</tbody>
</table>

* See Appendix below for explanation.

2. **Analogue 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


8. **IFRA Standard**

None.

9. **REACH Dossier**


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...
developmental toxicity was determined to be 100 mg/kg/day, the highest dosage tested 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 Geller, 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/cm²), and in a human maximization test at 20% (13,800 μg/cm²) (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 (1988b), RIFM (1979e), RIFM (1979f) and RIFM (1979g) 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

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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/m³; 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/m³) 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/m³) (1m³/1000L) = 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
day

Based on the IFRA survey results for hydroalcohols, 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/heatved oil plug-ins), the combined inhalation exposure would be 2.6 day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcohols 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.

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 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). 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 BCFAF 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/l (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 Eb50 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

<table>
<thead>
<tr>
<th>LC50 (Fish) (mg/L)</th>
<th>EC50 (Daphnia) (mg/L)</th>
<th>EC50 (Algae) (mg/L)</th>
<th>AF</th>
<th>PNEC (μg/L)</th>
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<tr>
<td>33.70</td>
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<td>19.117</td>
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RIFM Framework

Screening Level (Tier 1)

ECOSAR Acute Endpoints (Tier 2) Ver 1.11

ECOSAR Acute Endpoints (Tier 2) Ver 1.11

Tier 3: Measured Data

<table>
<thead>
<tr>
<th>LC50 (Fish)</th>
<th>EC50 (Daphnia)</th>
<th>NOEC</th>
<th>AF</th>
<th>PNEC</th>
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</tr>
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<tr>
<td>19.0</td>
<td>8.25</td>
<td>0.79</td>
<td>50</td>
<td>15.8</td>
<td></td>
</tr>
</tbody>
</table>

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/
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- 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?sessionid=0EF5C212B7906229F4774742A9A4D05B87
- US EPA Robust Summary: http://cfpub.epa.gov/hpv-s/
- 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-arqQS324GwbG&ved=0CBQ154

* 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
Q19. Open chain No
Q23. Aromatic No
Q24. Monocarbocyclic with simple substituents No
Q25. Cyclopolyoxyalkanes, etc. No
Q26. Monocycloalkanone or a bicyclic compound Yes Class Intermediate (Class II)

References


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