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RIFM fragrance ingredient safety assessment, *cis*-jasmone, CAS registry number 488-10-8

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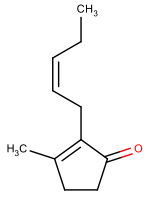
Name: *cis*-Jasmone

CAS Registry Number: 488-10-8

Additional CAS Numbers*:6261-18-3 *trans*-Jasmone (No Reported Use)



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*Included in this assessment because the materials are isomers.

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

cis-Jasmone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *cis*-jasmone is not genotoxic. Data on *cis*-jasmone provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for *cis*-jasmone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *cis*-jasmone is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to *cis*-jasmone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; *cis*-jasmone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2003; RIFM, 2013b)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day. (RIFM, 2015d)
Reproductive Toxicity: Developmental toxicity NOAEL = 250 mg/kg/day. Reproductive toxicity NOAEL = 750 mg/kg/day. (RIFM, 2015d)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.
RIFM (2018a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 94% (OECD 301 B) for CAS # 488-10-8	RIFM (1993)

Bioaccumulation:

Screening-level: 102.5 L/kg	(EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity:

Screening-level: 96-h Algae EC50: 14.69 mg/L	(ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 14.69 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 1.469 μg/L

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

1. Identification

1. Chemical Name: *cis*-Jasmone	**1. Chemical Name**: *trans*-Jasmone
2. CAS Registry Number: 488-10-8	**2. CAS Registry Number:** 6261-18-3
3. Synonyms: 3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one; 2-Cyclopenten-1-one, 3-methyl-2-(2Z)-2-pentenyl-; (Z)-3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one; 3-Methyl-2-(2-*cis*-pentenyl)-2-cyclopenten-1-one; *cis*-Jasmone	**3. Synonyms:** (E)-3-Methyl-2-(pent-2-enyl)cyclopent-2-en-1-one; *trans*-Jasmone; 2-Cyclopenten-1-one, 3-methyl-2-(2-pentenyl)-, (E)-; 3-Methyl-2-pent-2-en-1-ylcyclopent-2-en-1-one
4. Molecular Formula: $C_{11}H_{16}O$	**4. Molecular Formula:** $C_{11}H_{16}O$
5. Molecular Weight: 164.24	**5. Molecular Weight:** 164.24
6. RIFM Number: 908	**6. RIFM Number:** N/A
7. Stereochemistry: *Cis* isomer specified. One stereocenter and a total of 2 stereoisomers possible.	**7. Stereochemistry:** *Trans* isomer specified. One stereocenter and a total of 2 stereoisomers possible.

2. Physical data

1. Boiling Point: 146 °C (Fragrance Materials Association [FMA] Database), 256.01 °C (EPI Suite), 259 °C (533 K) at 1014 ± 10 hPa (RIFM, 2014)	**Boiling Point**: 256.01 °C (EPI Suite)
2. Flash Point: >200 °F; CC (FMA Database), >93 °C (Globally Harmonized System [GHS]), 116 °C (RIFM, 2014)	**Flash Point:** >93 °C (GHS)

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3. Log K_{OW}: 2.8 (RIFM, 1998b), 3.55 (EPI Suite)	**Log K_{OW}:** 3.5 (EPI Suite)
4. Melting Point: 40.24 °C (EPI Suite), less than −80 °C (193 K) at 1014 ± 10 hPa (RIFM, 2014)	**Melting Point**: 40.24 °C (EPI Suite)
5. Water Solubility: 60.54 mg/L (EPI Suite)	**Water Solubility:** 60.54 mg/L (EPI Suite)
6. Specific Gravity: 0.939–0.944 (Givaudan Specification Sheet, 1994), 0.941 (FMA Database)	**Specific Gravity:** Not available
7. Vapor Pressure: 0.0123 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg 20 °C (FMA Database), 0.0212 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.0212 mm Hg at 25 °C (EPI Suite)
8. UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Not available
9. Appearance/Organoleptic: Merck Index (1976), Arctander (Volume I, 1969): Pale yellowish or pale straw-colored, oily liquid. Diffusive, warm-spicy, somewhat fruit, but in dilution more floral odor of good tenacity. The pure material has notes reminiscent of celery, some find it bread-like, others find it fruity, waxy, etc.	**Appearance/Organoleptic:** Arctander (Volume I, 1969): Pale yellowish or pale straw-colored, oily liquid. Diffusive, sweet-fatty, somewhat floral, and slightly oily-fruity odor of good tenacity.

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015).

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.053% (RIFM, 2018b)
2. **Inhalation Exposure*:** 0.000084 mg/kg/day or 0.0061 mg/day (RIFM, 2018b)
3. **Total Systemic Exposure**:** 0.00091 mg/kg/day (RIFM, 2018b)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** III* (Expert Judgment)

Expert Judgment	Toxtree v3.1.0	OECD QSAR Toolbox v4.2
III	II	II

*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). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **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

7. Metabolism

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

8. Natural occurrence

cis-Jasmone is reported to occur in the following foods by the VCF*:

Apricot (*Prunus armeniaca* L.)
Beans
Beer
Camomile
Cinnamomum species
Citrus fruits
Curry (*Bergera koenigii* L.)
Mentha oils
Tea
Wormwood oil (*Artemisia absinthium* L.)

trans-Jasmone is reported to occur in the following foods by the VCF:

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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH dossier

Available for cis-jasmone; accessed 01/14/21 (ECHA, 2017). *trans*-Jasmone has been pre-registered for 2013; no dossier available as of 09/23/21.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *cis*-jasmone does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. *cis*-Jasmone was tested using the BlueScreen assay and found to be genotoxic with and without S9 metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. While the BlueScreen assay on the target material showed positive results, data from additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material. The mutagenic activity of *cis*-jasmone was assessed in a GLP-compliant Ames study conducted in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with *cis*-jasmone in dimethyl sulfoxide (DMSO) at concentrations up to 2500 μg/plate in the presence and absence of metabolic activation. No significant increase in the number of revertant colonies was detected in the strains at the concentrations tested (RIFM, 2003). Under the conditions of the study, *cis*-jasmone was considered not mutagenic in the Ames test.

The clastogenicity of *cis*-jasmone was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes (HPBL) were treated with *cis*-jasmone at concentrations up to 1643 μg/mL in the presence and absence of metabolic activation. No increase in the ratio of polychromatic erythrocytes was observed (RIFM, 2013b). Under the conditions of the study, *cis*-jasmone was considered negative for clastogenicity in human cells.

Based on the available data, *cis*-jasmone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/07/20.

11.1.2. Repeated dose toxicity

The MOE for *cis*-jasmone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on *cis*-jasmone to support the repeated dose toxicity endpoint. A dietary OECD 422 repeated dose toxicity combined with reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing test material *cis*-jasmone at doses of 0 (basic powdered diet), 1500, 5000, or 15000 ppm (equivalent to 0, 75, 250, or 750 mg/kg/day, as per the conversion factors for aged rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The animals were treated for 14 days before mating, throughout mating (total of 28 days for males), throughout gestation, and until day 4 postpartum for females. There was an overall statistically significant reduction in the terminal body weight for males at 5000 ppm (−8%) and 15000 ppm (−18% and −17% for males and females, respectively). The reduction in bodyweight gain was correlated with decreases in food consumption. There was an increase in the absolute and relative liver weights of all treated males and mid- and high-dose females, often reaching statistical significance. Hepatocyte hypertrophy was observed histopathologically in 4 mid-dose females and 7 high-dose (male and female) group animals. The liver weight increases were considered to be adaptive since there was no evidence of liver cell damage nor clinical chemistry alterations (Hall et al., 2012). The relative kidney weight increase was statistically significantly at 15000 ppm in males. The kidney of males at 5000 ppm (3/5) and 15000 ppm (all males) exhibited cortical tubular degeneration and/or regeneration. These kidney changes in males were confirmed with Martius Scarlet Blue staining and were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). There was a decrease in the absolute and relative thymus weights in males and females at 15000 ppm, which reached statistical significance for the females. This finding correlated with atrophy seen in 1 male and 3 females at 15000 ppm. This was considered likely to be a secondary effect due to bodyweight loss seen at this dose and the correlated stress. In the spleen, extramedullary hematopoiesis was increased in all treatment groups except for females at 15000 ppm, which correlated with a statistically significant decrease in spleen weight in females at this dose only. The absolute and relative adrenal weights were lower than the controls at 5000 and 15000 ppm in females, with no histopathological correlates. However, minimal or slight zona fasciculata vacuolation was observed in 4 of the 5 males at 15000 ppm. Thus, the NOAEL was considered to be 1500 ppm or 75 mg/kg/day, based on a statistically significant reduction in the terminal body weight of males and females in the higher dose groups and a decrease in the adrenal weights among females in the higher dose groups (RIFM, 2015d).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 75/3 or 25 mg/kg/day.

Therefore, the *cis*-jasmone MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-jasmone NOAEL in mg/kg/day by the total systemic exposure to *cis*-jasmone, 25/0.00091, or 27473.

In addition, the total systemic exposure to *cis*-jasmone (0.91 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/24/20.

11.1.3. Reproductive toxicity

The MOE for *cis*-jasmone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on *cis*-jasmone to support the developmental and reproductive toxicity endpoints. A dietary OECD 422 combined repeated dose toxicity with reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing test material, *cis*-jasmone at doses of 0 (basic powdered diet), 1500, 5000, or 15000 ppm (equivalent to 0, 75, 250, or 750 mg/kg/day, as per the conversion factors for aged rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The animals were treated for 14 days before mating, throughout mating (total of 28 days for males), throughout gestation, and until day 4 postpartum for the females. In addition to the systemic toxicity parameters, the developmental (number of pups born, pup survival, sex ratio, and pup weights) and reproductive (evaluation of the testes, spermatology, and estrous cycles) parameters were also assessed. Three females given 15000 ppm were euthanized following total litter loss postpartum. However, no treatment-related histopathological findings in the reproductive organs were observed on the 3 dams that could have caused the loss of the litters. At 15000 ppm, a treatment-related postnatal effect was observed on pup survival and growth. The viability index of pups at PND 4 was significantly lower (69.9%) than in the control (100%) and the historical control data range (94.1–100%) due to the 3 dams with total litter loss between PND 1–4. The terminal mean pup weight at PND 4 was statistically significantly decreased (−17%) when compared to the controls. The NOAEL for developmental toxicity was considered to be 5000 ppm

or 250 mg/kg/day, based on treatment-related effects on early postnatal development (pup mortality and reduced pup weight) in the 15000 ppm group, which were consistent with the severity of the maternal toxicity observed in the high-dose group. There were no treatment-related effects on mating performance, and fertility up to the highest-dose group tested. Thus, the NOAEL for fertility was considered to be 15000 ppm or 750 mg/kg/day, the highest dose tested (RIFM, 2015d).

Therefore, the *cis*-jasmone MOE for the developmental toxicity endpoint can be calculated by dividing the *cis*-jasmone NOAEL in mg/kg/day by the total systemic exposure to *cis*-jasmone, 250/0.00091, or 274725.

Therefore, the *cis*-jasmone MOE for the reproductive toxicity endpoint can be calculated by dividing the *cis*-jasmone NOAEL in mg/kg/day by the total systemic exposure to *cis*-jasmone, 750/0.0091, or 824176.

In addition, the total systemic exposure to *cis*-jasmone (0.91 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/06/20.

11.1.4. Skin sensitization

Existing data do not indicate that *cis*-jasmone is a sensitizer. *cis*-Jasmone does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, *cis*-jasmone is not a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). However, there are no *in vitro*, animal, or human data on *cis*-jasmone to support this prediction. In guinea pigs, an open epicutaneous test, Freund's Complete Adjuvant Test (FCAT), and a maximization test with *cis*-jasmone did not present reactions indicative of sensitization (Klecak, 1985; RIFM, 1978). In a human maximization test, no skin sensitization reactions were observed with *cis*-jasmone at 5520 μg/cm^2 (RIFM, 1977). In a Confirmation of No Induction in Humans test (CNIH) with 775 μg/cm^2 of *cis*-jasmone in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1972a). In another CNIH with 4000 μg/cm^2 *cis*-jasmone in 1:3 ethanol:diethylphthalate (1:3 EtOH:DEP), no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2018a).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, *cis*-jasmone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1971; Ishihara et al., 1986; RIFM, 1972b; RIFM, 1998b.

Literature Search and Risk Assessment Completed On: 12/22/20.

11.1.5. Phototoxicity/photoallergenicity

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

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/04/20.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on *cis*-jasmone. Based on the Creme RIFM Model, the inhalation exposure is 0.0061 mg/day. This exposure is 77.0 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *cis*-jasmone was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *cis*-jasmone was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify *cis*-jasmone as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in

EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), *cis*-jasmone presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. For CAS # 488-10-8.

RIFM, 1993: Inherent biodegradability of the test material was evaluated using the modified sealed vessel test following the OECD 301B method. The rate of degradation after 56 days was 94.3%.

RIFM, 1995: Ultimate biodegradability of the test material was evaluated using the sealed vessel test following the OECD 301B method. The rate of degradation after 28 days was 60%.

RIFM, 1998a: The Ready Biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F guidelines. Under the conditions of the study, biodegradation of 70% was observed after 31 days.

11.2.1.2.2. Ecotoxicity. For CAS # 488-10-8.

RIFM, 2015a: A fish (carp) acute toxicity study was conducted according to the OECD 203 method under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 54 mg/L.

RIFM, 2015b: A *Daphnia magna* acute immobilization test was conducted according to the OECD 203 method under static conditions. The calculated value of the 48-h EC50 value based on mean measured concentration was reported to be 45 mg/L (95% CI: 40–49 mg/L).

RIFM, 2015c: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 values based on nominal test concentration were reported to be 38 mg/L and 19 mg/L for growth rate and yield, respectively.

11.2.2. Other available data

cis-Jasmone has been registered for REACH with no additional data at this time.

11.2.2.1. Risk assessment refinement. Since *cis*-jasmone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.8	2.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volumes of Use for both CAS #s.

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

The RIFM PNEC is 1.469 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/12/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  - **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
  - **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
  - **IARC:** https://monographs.iarc.fr
  - **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
  - **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
  - **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	44.61			1000000	0.04461	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	40.98	21.25	14.69	10000	1.469	Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** v1.11	25.80	15.77	15.94			Neutral Organic SAR (Baseline toxicity)

&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission

- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/21/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix

Explanation of Cramer Classification:

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. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q15. Readily hydrolyzed? No.
Q19. Open chain? No.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No.
Q21. Three or more different functional groups? No.
Q44. Free α,β-unsaturated heteroatom? Yes Class III (Class high)

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