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# Update to RIFM fragrance ingredient safety assessment, linalool, CAS Registry number 78-70-6

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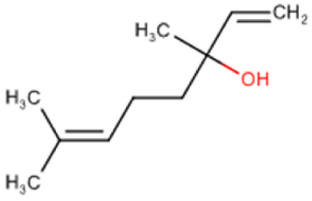


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Name: Linalool
CAS Registry Number: 78-70-6
Additional CAS Numbers:
126-91-0 *l*-Linalool
126-90-9 *d*-Linalool
*Included because the materials are isomers

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(*continued*)

**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
**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, 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, 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.**

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Linalool was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that linalool is not genotoxic. Data provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, developmental toxicity, and local respiratory toxicity endpoints. Data on read-across analog dehydrolinalool (CAS # 29171-20-8) provide a calculated MOE >100 for the fertility endpoint. Data show that there are no safety concerns for linalool for skin sensitization under the current declared levels of use; however, autoxidation products of this material are known to be contact allergens. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; linalool is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; linalool 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.

| **Human Health Safety Assessment** | |
|---|---|
| **Genotoxicity:** Not genotoxic. | RIFM (2010a) |
| **Repeated Dose Toxicity:** NOAEL = 200 mg/kg/day. | RIFM (1980) |
| **Reproductive Toxicity:** Developmental toxicity: NOAEL = 1000 mg/kg/day; Fertility: NOAEL = 750 mg/kg/day. | (Politano, 2008; ECHA REACH Dossier: Linalool; ECHA, 2011) |
| **Skin Sensitization:** Not Sensitizing (see note in section below). | (RIFM, 2010b; Skold, 2002; Skold, 2004; Urbisch, 2015; RIFM, 2005) |
| **Phototoxicity/Photoallergenicity:** Not phototoxic/not expected to be photoallergenic. | (UV/Vis Spectra; RIFM Database; RIFM, 1982a; RIFM, 1983a) |
| **Local Respiratory Toxicity:** NOAEC = 63 mg/m$^3$. | RIFM (2012) |

| **Environmental Safety Assessment** | |
|---|---|
| **Hazard Assessment:** | |
| **Persistence:** | |
| Critical Measured Value: 100% (302 B) for CAS # 78-70-6 | RIFM (1977) |
| **Bioaccumulation:** | |
| Screening-level: 42.33 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 20 mg/L | RIFM (1988a) |
| **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:** 48-h *Daphnia magna* EC50: 20 mg/L | RIFM (1988a) |
| **RIFM PNEC is:** 20 μg/L | |
| • Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1 | |

## 1. Identification

| Chemical Name: Linalool | Chemical Name: *l*-Linalool | Chemical Name: *d*-Linalool |
|---|---|---|
| **CAS Registry Number:** 78-70-6 | **CAS Registry Number:** 126-91-0 | **CAS Registry Number:** 126-90-9 |
| **Synonyms:** Coriandrol; 3,7-Dimethyl-1,6-octadien-3-ol; 2,6-Dimethyl-2,7-octadien-6-ol; Licareol; Linalol; 1,6-Octadien-3-ol, 3,7-dimethyl-; 2,7-Octadien-6-ol, 2,6-dimethyl-; Linalyl alcohol; 3,7-ｼﾞﾒﾁﾙ-1,6-ｵｸﾀﾀﾞｼﾞｴﾝ-3-ｵｰﾙ; 3,7-Dimethylocta-1,6-dien-3-ol; Petinerol; Farnesol KS; Linalool | **Synonyms:** (R)-3,7-Dimethyl-1,6-octadien-3-ol; 3,7-Dimethylocta-1,6-dien-3-ol; 1,6-Octadien-3-ol, 3,7-dimethyl-, (R)-; ３，７－ジメチル－１，６－オクタジエン－３－オール | **Synonyms:** (S)-3,7-Dimethyl-1,6-octadien-3-ol; 3,7-Dimethylocta-1,6-dien-3-ol; 1,6-Octadien-3-ol, 3,7-dimethyl-, (S)- |
| **Molecular Formula:** $C_{10}H_{18}O$ | **Molecular Formula:** $C_{10}H_{18}O$ | **Molecular Formula:** $C_{10}H_{18}O$ |
| **Molecular Weight:** 154.25 | **Molecular Weight:** 154.25 | **Molecular Weight:** 154.25 |
| **RIFM Number:** 128 | **RIFM Number:** 5160 | **RIFM Number:** 5159 |

## 2. Physical data*

1. **Boiling Point:** 198 °C (Fragrance Materials Association [FMA]), 0.2 mbar at 20 °C (RIFM, 1991a), 0.2 mbar at 20 °C (RIFM, 1991b), 204.05 °C (EPI Suite)
2. **Flash Point:** 160 °F; CC (FMA), 77 °C (Globally Harmonized System)
3. **Log $K_{OW}$:** 3.28 ± 0.26 (Cal, 2006a), 2.84 at 25 °C (RIFM, 1988c), 2.9 (RIFM, 1991a), 2.9 (RIFM, 1991b), 3.38 (EPI Suite)
4. **Melting Point**: <20 °C (RIFM, 1991c; RIFM, 1991b; RIFM, 1991a), −11.39 °C (EPI Suite)
5. **Water Solubility:** 1450 (20 °C; RIFM, 1991b)
6. **Specific Gravity:** 0.861 g/mL at 20 °C (RIFM, 1991c), 0.860–0.864 (FMA), 0.858–0.862 (FMA), 0.861 g/mL at 20 °C (RIFM, 1991b), 0.862 (RIFM, 1989a), 0.861 g/mL at 20 °C (RIFM, 1991a), 0.86 g/mL (RIFM, 1994a)
7. **Vapor Pressure:** 0.0521 mm Hg at 20 °C (EPI Suite v4.0), 0.05 mm Hg at 20 °C (FMA), 0.0832 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to very pale yellow liquid with a refreshing, floral, woody odor similar to that of bergamot oil and French lavender* (Arctander, 1969).

*Physical data is identical for all materials included in this assessment.

## 3. Volume of use (worldwide band)

1. >1000 metric tons per year (IFRA, 2015)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 1.06% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0032 mg/kg/day or 0.23 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.025 mg/kg/day (RIFM, 2019)

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics or 97.5th percentile, inhalation exposure, and total exposure.

## 5. Derivation of systemic absorption

1. Dermal: 80%

**RIFM, 2007a (data also available in RIFM, 2007b; RIFM, 2007c; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; RIFM, 2007d; RIFM, 2008d):** A series of *in vitro* human skin penetration studies was conducted with 4% linalool under in-use (unoccluded) and occluded conditions in diethyl phthalate (DEP), dipropylene glycol (DPG), ethanol/water, petrolatum, ethanol/DEP, or ethanol/DPG vehicles. Twelve active dosed diffusion cells were prepared from 7 donors for each application condition (unoccluded, occluded, and an unoccluded control cell). Epidermal membranes were used, and their integrity was assessed by measuring the permeation rate of tritiated water over a period of 1 h. Permeation of linalool from a 5 μL/$cm^2$ dose was then measured at 12 time points over 24 h. Occluded conditions reduced the loss of volatile application vehicles and test compounds but may have also increased skin hydration, factors which caused a significant increase in the permeation of linalool. Under unoccluded experimental conditions, there was a gradual but comprehensive evaporative loss (approximately 97% evaporative loss over 24 h, with less than 7% recovery within the first hour of analysis). Total absorbed dose values from an unoccluded application ranged from 1.8% to 3.57% (DPG < ethanol/DPG < ethanol/DEP < DEP < petrolatum < ethanol/water). Total absorbed dose values from an occluded application ranged from 5.73% to 14.4% (DEP < ethanol/DEP < DPG < petrolatum < ethanol/DPG < ethanol/water). The most conservative dermal penetration of 14.4% was determined. However, the total recovery reported was 8.01% ± 0.69% and 36.3% ± 2.9%, respectively, for the unoccluded and occluded applications. Since the evaporative loss was rapid, and there was a poor recovery of the test material, the study was not used towards the safety assessment. Data from RIFM's *in silico* skin absorption model (RIFM, 2014) were used to predict the dermal penetration of 80% for linalool, as shown below.

| Name | Linalool |
|---|---|
| $J_{max}$ (μg/$cm^2$/h) | 121.08[1] |
| Skin Absorption Class | 80% |

[1] $J_{max}$ was calculated based on measured log $K_{ow}$ = 2.9 (RIFM, 1991b) and water solubility = 1450 mg/L at 20 °C (RIFM, 1991b).

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

## 6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low* (Expert Judgment)

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| I | III | I |

*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:** Dehydrolinalool (CAS # 29171-20-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 7. Metabolism

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

## 8. Natural occurrence

Linalool is reported to occur in the following foods by the VCF*:

Citrus fruits
Mastic (*Pistacia Lentiscus*)

Mentha oils
*Ocimum* species
*Salvia* species
Tea
Tomato (*Lycopersicon esculentum* Mill.)
*Vaccinium* species
Wine
Wormwood Oil (*Artemisia absinthium* L.)
*l*-Linalool is reported to occur in the following foods by the VCF:
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Beer
*Cinnamomum* species
Citrus fruits
*Mangifera* species
Rum
Salami
Sugar molasses
Tea
*d*-Linalool is reported to occur in the following foods by the VCF:
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Beer
*Cinnamomum* species
Citrus fruits
Fennel (*Foeniculum vulg.*, ssp. *capillaceum*; var.)
*Mangifera* species
Rum
Sugar molasses
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; accessed 09/27/21 (ECHA, 2011).

## 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, linalool does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* *l*-Linalool was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic potential of linalool has been evaluated in bacteria and in cultured mouse L5718Y tk ±cells. The Fragrance Material Review on linalool (RIFM, 2003a) summarizes available data, including negative Ames studies with *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537, TA1538, and *E. coil* strain WP2uvrA, a negative sister chromatid exchange assay in CHO cells, and a negative test for the induction of unscheduled DNA synthesis in rat primary hepatocytes. Additionally, the US NTP has shown linalool to be non-mutagenic in *S. typhimurium* strains TA100, 1535, 97, 98, 102, and 104 up to 1000 μg/plate (NTP, 1999). Mammalian mutagenicity was evaluated in 1 mouse lymphoma assay that demonstrated a weak positive result for linalool; however, the authors emphasized that positive results in this assay are commonly observed for polar substances in the presence of S9 and may be associated with changes in physiologic culture conditions such as pH and osmolality (Heck, 1989). When a second mouse lymphoma study was conducted, which took into account cytotoxicity, osmolality, and pH, the results were negative (RIFM, 1994b).

Linalool was assessed for clastogenicity in a chromosome aberration study and an *in vivo* micronucleus test. Linalool was assessed in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. Groups of male and female Swiss CD-1 mice were administered a single dose of linalool in corn oil via oral gavage at doses of 500, 100, or 1500 mg/kg body weight. The bone marrow of the treated groups was sampled 24 or 48 h after dosing. No increase in the frequency of micronucleated polychromatic erythrocytes was observed in the polychromatic erythrocytes of the bone marrow of animals treated with linalool (RIFM, 2001). In an *in vitro* chromosome aberration assay, linalool did not induce significant increases in chromosome aberrations and was concluded to be negative (RIFM, 1983b). An *in vitro* micronucleus test demonstrated negative effects for linalool (DiSotto, 2011), further supporting a lack of genotoxic concern.

Linalool was also reviewed by the Expert Panel for Fragrance Safety*, and it was concluded that the mutagenicity and clastogenicity data are sufficient to indicate that linalool is not genotoxic (RIFM, 2010a).

*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:** DiSotto (2008); Mitic-Culafic (2009); Lutz (1980); Eder (1982a); Ishidate (1984); Oda (1978); Kuroda (1984); Yoo (1986); Mademtzoglou (2011); DiSotto (2011); RIFM, 1982b; RIFM, 1994b; Eder (1980); Eder (1982b); RIFM, 1983c.

**Literature Search and Risk Assessment Completed On:** 03/11/21.

#### *11.1.2. Repeated dose toxicity*

The MOE for linalool is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* The repeated dose toxicity data on linalool are sufficient for the repeated dose toxicity endpoint. A dermal, 90-day (13-week), subchronic toxicity study was conducted in rats. Applications with linalool at doses of 250, 1000, and 4000 mg/kg/day were made daily to the clipped and shaved backs of the animals. The NOAEL was determined to be 250 mg/kg/day, based on reduced body weights among animals of the higher dose groups and mortality among the high-dose group animals (RIFM, 1980). An *in vitro* dermal penetration study was conducted with linalool (see Section VI) under occlusion and non-occlusion, resulting in significant evaporation of linalool and a dermal absorption value of 14.4% and 3.57% under occlusion and non-occlusion conditions (RIFM, 2007a). Since the evaporative loss from the skin absorption study was significantly high, the results from the study were not considered for the safety assessment on linalool. The SAM model prediction (RIFM, 2014; see Section VI) suggests a dermal absorption value of 80%. The more conservative SAM model prediction for dermal absorption was considered for calculating the dermal bioavailability for linalool. Thus, to account for bioavailability following dermal application, data from RIFM's *in silico* SAM model were used to revise the NOAEL of 250 mg/kg/day to reflect the systemic dose. At a

predicted dermal penetration of 80% of the applied dose, the revised linalool toxicity NOAEL from the dermal study is 200 mg/kg/day. **Therefore, the linalool MOE for the repeated dose toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure to linalool, 200/0.025, or 8000.**

When correcting for skin absorption, the total systemic exposure to linalool (25 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** RIFM, 2003a; RIFM, 2008e; RIFM, 2008f; RIFM, 2008g; Bickers (2003); RIFM, 2008h; RIFM, 2010a; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner (1973); RIFM, 2013b; Hood (1978); Howes (2002); Jirovetz (1990); Jirovetz (1991); Parke (1974); Green (1996); Meesters (2007); Chadha (1982); Chadha (1984); RIFM, 1998a; Jager (1992); Schmitt (2010); Meyer (1959); Cal (2006b); Cal (2006c); Cal (2003); Meyer (1965); RIFM, 2010c; RIFM, 1989b; RIFM, 1990; Al-Said (1987); Matsui (1967).

**Literature Search and Risk Assessment Completed On:** 02/16/21.

*11.1.3. Reproductive toxicity*

The MOE for linalool is adequate for the reproductive toxicity endpoint at the current level of use.

*11.1.3.1. Risk assessment.* The developmental toxicity data on linalool are sufficient for the developmental toxicity endpoint. A gavage developmental toxicity study was conducted on rats that received oral doses of linalool at 0, 250, 500, or 1000 mg/kg/day in corn oil on gestation days 7–17, which resulted in a NOAEL of 1000 mg/kg/day for developmental toxicity, the highest dosage tested (Politano, 2008). **Therefore, the linalool MOE for the developmental toxicity endpoint can be calculated by dividing the linalool NOAEL in mg/kg/day by the total systemic exposure to linalool, 1000/0.025, or 40000.**

There are no fertility data on linalool. Read-across material dehydrolinalool (CAS # 29171-20-8; see Section VI) has a gavage reproductive toxicity screening study (equivalent to OECD 421) conducted in rats. The animals were given the test material at doses of 0 (rapeseed oil), 50, 200, or 750 mg/kg/day. The NOAEL was determined to be 750 mg/kg/day since there were no adverse effects of treatment on mating and fertility of males and females at the highest dose tested (ECHA, 2011). In a dermal, 90-day (13-week), subchronic toxicity study with linalool in rats (RIFM, 1980), in addition to the systemic endpoint, organ weights (testes and ovaries) and histopathology (testes, epididymis, ovaries, pituitary, and thyroid) were performed on the reproductive organs, and no effects were observed. Together, these data indicate no concern for reproductive toxicity. Thus, a NOAEL of 750 mg/kg/day derived from the OECD 421 study conducted on read-across material dehydrolinalool was selected for the reproductive toxicity endpoint. **Therefore, the linalool MOE for the reproductive toxicity endpoint can be calculated by dividing the dehydrolinalool NOAEL in mg/kg/day by the total systemic exposure to linalool, 750/0.025, or 30000.**

When correcting for skin absorption, the total systemic exposure to linalool (25 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** RIFM, 2003a; RIFM, 2008e; RIFM, 2008f; RIFM, 2008g; Bickers (2003); RIFM, 2008h; RIFM, 2010a; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner (1973); RIFM, 2013b; Hood (1978); Howes (2002); Jirovetz (1990); Jirovetz (1991); Parke (1974); Green (1996); Meesters (2007); Chadha (1982); Chadha (1984); RIFM, 1998a; Jager (1992); Schmitt (2010); Meyer (1959); Cal (2006b); Cal (2006c); Cal (2003); Meyer (1965); RIFM, 2010c; RIFM, 1989b; RIFM, 1990; Al-Said (1987); Matsui (1967); RIFM, 2006; Letizia (2007).

**Literature Search and Risk Assessment Completed On:** 03/05/21.

*11.1.4. Skin sensitization*

Based on the existing data, linalool does not present a concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk assessment.* Based on the available data, linalool does not present a concern for skin sensitization. Linalool is not predicted to be directly reactive to skin proteins (Roberts, 2007; OECD Toolbox v4.2; Toxtree v3.1.0). However, the autoxidation products of linalool are protein reactive based on *in vivo* skin sensitization data (Skold, 2004)*. Linalool was found to be negative in *in vitro* Direct Peptide Reactivity Assay (DPRA) and KeratinoSens but positive in human cell line activation test (h-CLAT) and U937-CD86 test (Urbisch, 2015). In guinea pig test methods and the local lymph node assay (LLNA), positive and negative results have been reported (RIFM, 2016; Basketter, 2002a; Basketter, 2002b; Ishihara, 1986; Klecak, 1985; Sharp, 1978; Skold, 2004). In these LLNAs and guinea pig studies, the positive results have been shown to be the result of sensitizing products of autoxidation and irritation (RIFM, 2010b; Skold, 2002; Skold, 2004). In a Confirmation of No Induction in Humans (CNIH) test, no reactions indicative of sensitization have been observed to linalool at the maximum tested concentration of 12.7% (14998 μg/cm$^2$) (RIFM, 2005). Similarly, no reactions were observed in the human maximization test with 20% (13800 μg/cm$^2$) linalool in petrolatum (RIFM, 1975). Based on the weight of evidence, linalool, in the absence of oxidation, does not present a concern for skin sensitization.

*Note: Whereas linalool in the absence of oxidation is not considered to be a sensitizer, autoxidation products of this material are known to be contact allergens. Linalool, and natural products rich in linalool, are subject to an IFRA Standard that defines a good manufacturing practice specification limiting peroxide levels to 20 mmol/L with a recommendation to add an antioxidant at the time of production (IFRA, 2004).

**Additional References:** RIFM, 1964; Hostynek (2007); Greif (1967); Ryan (2000); Gerberick (2004); Basketter (2003).

**Literature Search and Risk Assessment Completed On:** 03/11/21.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the UV/Vis absorbance spectra and available study data, linalool would not be expected to present a concern for phototoxicity. Based on the UV/Vis absorbance spectra, linalool would not be expected to present a concern for photoallergenicity.

*11.1.5.1. Risk assessment.* UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In human and guinea pig studies, no reactions indicative of phototoxic responses were observed (RIFM, 1982a; RIFM, 1983a). Based on the lack of absorbance and study data, linalool does not present a concern for phototoxicity. Based on lack of absorbance, linalool does not present a concern for photoallergenicity.

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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, 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 03/02/21.

*11.1.6. Local respiratory toxicity*

The MOE for linalool is adequate for the local respiratory toxicity endpoint at the current level of use.

*11.1.6.1. Risk assessment.* The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week acute inhalation study conducted in rats, a NOAEC of 63 mg/m$^3$ was reported for linalool (RIFM, 2012). Treatment-related effects were limited to non-adverse microscopic findings in the nasal cavity. Inflammation and epithelial (squamous and transitional) hyperplasia in nasal level 1 of males and females, as well as subacute inflammation of nasal level 3 in females, were considered exacerbated background lesions as they were also observed in control group males and females and were not considered adverse. Other epithelial findings in nasal level 1 of males and females, inflammation, and/or epithelial changes in nasal levels 2 and 3 in males and nasal level 2 in females had similar incidences in the control and treatment-exposed groups.

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

- (63 mg/m$^3$) × (1 m$^3$/1000 L) = 0.063 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.063 mg/L) (61.2 L/d) = 3.86 mg/d
- (3.86 mg/d)/(0.0016 kg lung weight of rat*) = 2412.5 mg/kg/day

The 95th percentile calculated exposure was reported to be 0.23 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015). 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, 2009) to give 0.35 mg/kg lung weight/day resulting in a MOE of 6892.9 (i.e., [2412.5 mg/kg lung weight/day]/[0.35 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.23 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

**Additional References:** Troy (1977): Jirovetz (1991); Buchbauer (1991); Jirovetz (1990); UGCM, 1997; Buchbauer (1993); Perrucci (1996); Perrucci (1995a); Rice (1994a); Silver (1992); Karr (1992); Regnault-Roger (1995); Rice (1994b); Perrucci (1995b); Sugawara (1998); Coats (1991); Cometto-Muniz (1998); RIFM, 2003b; RIFM, 2003c; Rogers (2003a); RIFM, 2003d; RIFM, 2003e; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola (2004a); Barocelli (2004); Rogers (2005); Kuroda et al., 2005; Tanida et al., 2006; Yang et al., 2005; Corsi et al., 2007; Sato et al., 2007; Nakamura et al., 2010; Nakamura et al., 2009; de Moura Linck et al., 2009; RIFM, 2013b; Vethanayagam et al., 2013.

**Literature Search and Risk Assessment Completed On:** 03/12/21.

### *11.2. Environmental endpoint summary*

#### *11.2.1. Screening-level assessment*

A screening-level risk assessment of linalool was performed following the RIFM Environmental Framework (Salvito et al., 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, linalool 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 is $> 1$).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify linalool 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.

#### *11.2.2. Risk assessment*

Based on the current Volume of Use (2015), linalool presents a risk to the aquatic compartment in the screening-level assessment.

##### *11.2.2.1. Key studies*

*11.2.2.1.1. Biodegradation.* For CAS # 78-70-6.

**RIFM, 1977:** The ultimate inherent biodegradability of the test material was evaluated using the Zahn Wellens test according to the OECD Guideline 302B. Mean biodegradation degree (DOC) after 13 days was reported to be 90%–100%.

**RIFM, 1994a:** The ultimate biodegradability of the test material was evaluated using the sealed vessel test according to the OECD Guideline 301B. Biodegradation of 97.1% was observed after 28 days.

**RIFM, 1991c:** The ready biodegradability of the test material was evaluated using the modified MITI test according to OECD Guideline 301C. Biodegradation of 80% was observed after 28 days.

*11.2.2.1.2. Ecotoxicity.* For CAS # 78-70-6.

**RIFM, 1998b:** The 96-h algae growth inhibition study was conducted using fluorescence. At the end of the study, the $E_\mu C50$ (growth rate) was reported to be 141.4 mg/L (95% CI: 92.2–216.8 mg/L), and the $E_B C50$ (yield) was reported to be 85.9 mg/L (95% CI: 47–157 mg/L).

**RIFM, 1998a:** The *Daphnia magna* immobilization study was conducted according to the DIN 38412 L11 guideline. The 48-h EC50 was reported as 20 mg/L (nominal concentration).

**RIFM, 1991d:** The acute fish (Rainbow trout) toxicity test was conducted according to the OECD 203 guideline under static conditions. The reported 96-h LC50 was 27.8 mg/L (95% CI: 22.9–33.7 mg/L) based on average measured concentration.

**RIFM, 1989c:** The acute fish (Golden Orfe) toxicity test was conducted following DIN 38412 guideline under flow-through conditions. The 96-h LC50 value based on nominal test concentration was reported to be greater than 21.5 mg/L but less than 46.4 mg/L.

*11.2.2.1.3. Other available data.* Linalool (CAS # 78-70-6) has been registered for REACH, and the following additional information is available at this time:

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guideline. Biodegradation of 64% was observed after 28 days.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on mean measured concentration was reported to be 59 mg/L.

The algae growth inhibition test was conducted according to the DIN 38412 L9 guideline under static conditions. The 72-h EC50 values based on nominal test concentration for growth rate and biomass were reported to be 156.7 mg/L and 88.3 mg/L, respectively.

*11.2.3. 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.

Note: The difference between the RIFM PNEC and the REACH PNEC is due to the use, in REACH, of an Assessment Factor of 100 for the same lowest endpoint that RIFM uses, an Assessment Factor of 1000. It was previously acceptable to use the algae NOEC as a single chronic value (and thus the lower Assessment Factor). In this current assessment, a lower Assessment Factor would require either a *Daphnia* or fish chronic alone or in combination with algae (or the use of all 3 species). None of this, however, changes the outcome of the risk assessment; all PEC/PNECs are <1.

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 2.90 | 2.90 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band* | >1000 | >1000 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

*Combined volumes for all CAS #

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

The RIFM PNEC is 20 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:** 03/12/21.

## 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&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 09/27/21.

## Declaration of competing interest

The authors declare that they have no known competing financial

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 34.3 | | | 1000000 | 0.034 | |
| ECOSAR Acute Endpoints **(Tier 2)** v1.11 | 2.191 | 0.329 | 6.863 | 10000 | 0.0329 | Vinyl/Allyl Alcohols |
| ECOSAR Acute Endpoints **(Tier 2)** | 19.704 | 12.517 | 12.769 | | | Neutral organics |

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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112687.

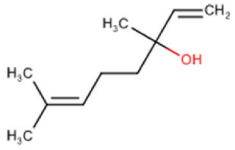
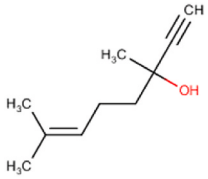
## Appendix

*Read-across Justification*

*Methods*

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

| | Target material | Read-across material |
|---|---|---|
| **Principal Name** | Linalool | Dehydrolinalool |
| **CAS No.** | **78–70–6** and 126-91-0 | 29171-20-8 |
| **Structure** |  |  |
| **Similarity (Tanimoto score)** | | 0.50 |
| **Read-across Endpoint** | | • Fertility |
| **Molecular Formula** | C10H18O | C10H16O |
| **Molecular Weight** | 154.253 | 152.237 |
| **Melting Point (°C, EPI Suite)** | −11.39 | 15.40 |
| **Boiling Point (°C, EPI Suite)** | 198.00 | 212.37 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 2.13E+01 | 4.64E+00 |
| **Log $K_{ow}$ (KOWWIN v1.68 in EPI Suite)** | 2.9 (measured; RIFM, 1991b) | 2.75 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 1450 (measured; 20 °C; RIFM, 1991b) | 1.08E+03 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 121.08 (calculated based on measured log Kow and measured water solubility) | 66.24 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 2.18E+00 | 4.49E-01 |
| | ***Reproductive toxicity*** | |
| **ER Binding by OECD QSAR Tool Box (4.2)** | • Non-binder, non-cyclic structure | • Non-binder, non-cyclic structure |
| **Developmental Toxicity Model by CAESAR v2.1.6** | • Non-toxicant (low reliability) | • Non-toxicant (low reliability) |
| | ***Metabolism*** | |
| **OECD QSAR Toolbox (4.2) Rat liver S9 metabolism simulator** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on linalool (CAS # 78-70-6). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, read-across analog dehydrolinalool (CAS # 29171-20-8) was identified as a read-across material with sufficient data for toxicological evaluation.

*Conclusions*

- Dehydrolinalool (CAS # 29171-20-8) was used as a read-across analog for the target material linalool (CAS # 78-70-6) for the fertility endpoint.
  - o The target material and the read-across analog belong to the structural class of $\alpha,\beta$ unsaturated tertiary alcohols.
  - o The target material and the read-across analog have a 6-methyl-2-heptenol fragment common among them.
  - o The key difference between the target material and the read-across analog is that the target has a double bond in the $\alpha$-$\beta$ position, whereas the read-across material has a triple bond in the $\alpha$-$\beta$ unsaturation. This structural difference between the target material and the read-across analog does not raise additional structural alerts, so the structural differences are not relevant from a toxic endpoint perspective.
  - o The target material and the read-across analog have a Tanimoto score, as mentioned in the above table. The Tanimoto score is mainly driven by the 6-methyl-2-heptenol fragment. The differences in the structure that is responsible for the Tanimoto score $<1$ are not relevant from a toxicological endpoint perspective.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the fertility endpoint.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the reproductive toxicity endpoint are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the fertility endpoint are consistent between the metabolites of the read-across analog and the target material.

*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, and divalent S? No
Q43. Possibly harmful divalent sulfur (not detected via Q3) No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q42. Possibly harmful analog of benzene? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? Yes
Q18. One of the list (see Cramer et al., 1978 for detailed explanation on list of categories)? No, Low (Class I)

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