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RIFM fragrance ingredient safety assessment, hydroxycitronellal, CAS Registry Number 107-75-5

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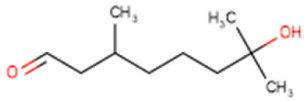

Version: 100821. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Hydroxycitronellal

CAS Registry Number: 107-75-5

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., 2017; Safford et al., 2015a, 2017; Comiskey 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

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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.

Hydroxycitronellal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2) show that hydroxycitronellal is not expected to be genotoxic. Data on hydroxycitronellal provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided hydroxycitronellal a No Expected Sensitization Induction Level (NESIL) of 4900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/violet (UV/Vis) spectra; hydroxycitronellal is not expected to be phototoxic/photoallergenic. Data on hydroxycitronellal provide a calculated MOE >100 for the local respiratory endpoint. The environmental endpoints were evaluated; hydroxycitronellal 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 expected to be genotoxic.	(RIFM, 2014b; RIFM, 2016b; RIFM, 2016c; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 99 mg/kg/day.	RIFM, (2020c)
Reproductive Toxicity: Developmental toxicity NOAEL = 297 mg/kg/day; Fertility NOAEL = 297 mg/kg/day.	RIFM, (2020c)
Skin Sensitization: NESIL = 4900 μg/cm^2.	RIFM, (2006a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 70 mg/m^3.	RIFM, (2013)

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 93.7% (OECD 301B)	RIFM, (1994)
Bioaccumulation:	
Screening-level: 11.52 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 8.586 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 et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 8.586 mg/L	(ECOSAR; US EPA, 2012b
RIFM PNEC is: 0.8586 μg/L	

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

1. Identification

1. **Chemical Name:** Hydroxycitronellal
2. **CAS Registry Number:** 107-75-5
3. **Synonyms:** Citronellalhydrate; 3,7-Dimethyl-7-hydroxyoctanal; Laurinal; Laurine; Octanal, 7-hydroxy-3,7-dimethyl; Oxy-dihydrocitronellal; ﾋﾄﾞﾛｷｼｼﾄﾛﾈﾗｰﾙ; 7-Hydroxy-3,7-dimethyloctanal; L-laurinal; L-Hydroxycitronellal; Hydroxycitronellal
4. **Molecular Formula:** $C_{10}H_{20}O_2$
5. **Molecular Weight:** 172.26

6. **RIFM Number:** 126
7. **Stereochemistry:** Isomer not specified. One chiral center present, and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 241 °C (Fragrance Materials Association [FMA]), 241.19 °C (EPI Suite)
2. **Flash Point:** >100 °C (Globally Harmonized System), >212 °F; CC (FMA)
3. **Log K_{OW}:** 1.76 (RIFM, 2003e), 1.68 at 25 °C - 1.70 (RIFM, 1989e), 1.5 (Procter and Gamble Company, 1996), 2.11 (EPI Suite), 2.11 (RIFM, 2018)
4. **Melting Point**: < −100 °C (RIFM, 2012), 23.36 °C (EPI Suite)
5. **Water Solubility:** 34.7 g/L at 20 ± 0.5 °C (RIFM, 2003e), 3042 mg/L (EPI Suite)
6. **Specific Gravity:** 0.93 g/mL (RIFM, 1994), 0.920–0.925 (FMA), 0.918–0.923 (FMA)
7. **Vapor Pressure:** 0.00338 mm Hg at 20 °C (EPI Suite v4.0), 0.001 mm Hg at 20 °C (FMA), 0.0058 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:** Arctander (1969): Colorless, oily, or viscous liquid. Sweet-floral, at first delicate and refreshingly mild, but often increasing in odor strength after a short olfactory study. The floral notes are mild, light, and resemble the lily of the valley. The tenacity is good, and the odor diffusion increases significantly when the material is properly blended with lower boiling odorants or modifiers. Sweet-floral taste but shows a bitter aftertaste at concentrations higher than 20 ppm, sometimes even much lower than that.

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.64% (RIFM, 2019a)
2. **Inhalation Exposure*:** 0.0011 mg/kg/day or 0.081 mg/day (RIFM, 2019a)
3. **Total Systemic Exposure**:** 0.013 mg/kg/day (RIFM, 2019a)

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

6.1. *Cramer classification*

Class I, Low (Expert Judgment)

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

*See the Appendix below for further details.

6.2. *Analogs selected*

a. **Genotoxicity:** 6-Methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2)
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: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Pepper (*Piper nigrum* L.)

*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.

9. REACH dossier

Available; accessed 10/08/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for hydroxycitronellal are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.38
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	2.3
4	Products related to fine fragrances	2.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.53
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.53
5C		0.53

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	
5D	Baby cream, oil, talc	0.18
6	Products with oral and lip exposure	1.2
7	Products applied to the hair with some hand contact	1.6
8	Products with significant ano-genital exposure (tampon)	0.18
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.1
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.78
10B	Aerosol air freshener	7.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.18
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	100

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For hydroxycitronellal, the basis was the reference dose of 0.99 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 4900 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, hydroxycitronellal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of hydroxycitronellal; however, read-across can be made to 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2; see Section VI). The mutagenic activity of 6-methoxy-2,6-dimethylheptan-1-al has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 6-methoxy-2,6-dimethylheptan-1-al in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014b). Under the conditions of the study, 6-methoxy-2,6-dimethylheptan-1-al was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of hydroxycitronellal; however, read-across can be made to 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2; see Section VI). The clastogenic activity of 6-methoxy-2,6-dimethylheptan-1-al was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 6-methoxy-2,6-dimethylheptan-1-al in DMSO at concentrations of up to 1723 μg/mL in the presence and absence of S9 for 3 h and in the absence of metabolic activation for 24 h. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at all 3 evaluated concentrations of the 3-h treatment without S9 and at the highest evaluated concentration (1723 μg/mL) of the 3-h treatment with S9. No statistically significant increase in the BNMN frequency was observed at any evaluated concentration in the approximate 24-h treatment without S9 (RIFM, 2016b). Under the conditions of the study, 6-Methoxy-2,6-dimethylheptan-1-al was considered positive for clastogenic activity in the *in vitro* micronucleus test.

As a follow-up to the positive *in vitro* MNT assay, a GLP-compliant 3D reconstructed skin micronucleus assay (RSMN) was conducted to evaluate the genotoxic potential of 6-methoxy-2,6-dimethylheptan-1-al in EpiDerm. Acetone was used as the vehicle. EpiDerm tissues were treated with 6-methoxy-2,6-dimethylheptan-1-al at 24-h intervals for 48 and 72 h, at concentrations up to 45 mg/mL. No increase in the number of binucleated cells with micronuclei was observed when tested up to the maximum dose (RIFM, 2016c). Under the conditions of the study, 6-methoxy-2,6-dimethylheptan-1-al was concluded to be negative for the induction of micronuclei in the reconstructed skin micronucleus assay (RSMN) using the EpiDerm model.

To investigate the biological and systemic relevance of the *in vitro* MNT assay, the clastogenic activity of 6-methoxy-2,6-dimethylheptan-1-al was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474.6-Methoxy-2,6-dimethylheptan-1-al was administered in corn oil to groups of male and female CD-1 mice at doses of 500, 1000, and 2000 mg/kg were. Mice from each dose level were euthanized at both 24- and 48-h time points, at which time the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow compared to vehicle control (RIFM, 2016a). Under the conditions of the study, test 6-methoxy-2,6-dimethylheptan-1-al was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 6-methoxy-2,6-dimethylheptan-1-al does not present a concern for genotoxic potential, and this can be extended to hydroxycitronellal.

Additional References: Wild et al., 1983.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

The MOE for hydroxycitronellal 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 hydroxycitronellal. In a GLP and OECD 422-compliant study, 10 Wistar rats/sex/dose were administered hydroxycitronellal via drinking water at concentrations of 0, 1500, 5000, and 15000 ppm (equivalent to 0, 94, 297, and 770 mg/kg/day in males, and 0, 150, 492, and 1073 mg/kg/day in females, according to the study report). Both sexes were treated for a 2-week, pre-mating period and 2-week mating period, and females continued to be treated throughout gestation and lactation. No treatment-related mortality occurred throughout the study period. No treatment-related adverse effects were observed in functional observations, motor activity, hematology, clinical chemistry, thyroid hormones, necropsy, or histopathology. Water consumption, food consumption, body weight, and bodyweight gain were significantly reduced in both sexes at the high dose through most of the study period. Based on reduced food consumption and body weights in both sexes at 15000 ppm, the NOAEL for this study was determined to be 5000 ppm, equivalent to 297 mg/kg/day in males and 492 mg/kg/day in females (RIFM, 2020c).

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 297/3 or 99 mg/kg/day.

Therefore, the hydroxycitronellal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,5,5-trimethylhexanal NOAEL in mg/kg/day by the total systemic exposure for Hydroxycitronellal, 99/0.013 or 7615.

In addition, the total systemic exposure to Hydroxycitronellal (13 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose (RfD) of 0.99 mg/kg/day.

Derivation of RfD

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for hydroxycitronellal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 99 mg/kg/day by the uncertainty factor, 100 = 0.99 mg/kg/day.

*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: 05/13/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on hydroxycitronellal. In an OECD 422/GLP-compliant study, groups of 10 Wistar rats/sex/dose were administered hydroxycitronellal at concentrations of 0, 1500, 5000, and 15000 ppm (mg/kg/day equivalency in males: 0, 94, 297, and 770; in females: 0, 150, 492, and 1073) through drinking water. Males were treated for 33 days (2 weeks prior to mating, during mating, and until study completion), and females were treated for 41–57 days (2 weeks prior to mating, during mating, and up to lactation day 4). No animal mortality was reported at any dose level during the study. However, in the highest-dose group, 1 male and 1 female were euthanized due to their poor overall condition. Significantly reduced bodyweight gains were observed in males and females during pre-mating (0–13 days), followed by bodyweight loss (0–7 days) in the highest dose. The gestation index was significantly reduced, and post-implantation loss was significantly increased at 15000 ppm. No treatment-related effects were seen on other reproductive parameters: mating, fertility and conception indices, precoital time, and numbers of corpora lutea. No histopathological changes were observed at any dose groups. With respect to developmental toxicity, pups at 15000 ppm (both sexes) had significantly lower body weights than controls. In addition, the viability index was significantly reduced at the highest dose level. Thus, the NOAEL for developmental toxicity and fertility was considered to be 5000 ppm (equivalent to 297 mg/kg/day), based on reduced gestation index and decrease in pup body weight and viability index at 15000 ppm (RIFM, 2020c).

Therefore, the hydroxycitronellal MOE for the reproductive toxicity endpoint can be calculated by dividing the hydroxycitronellal NOAEL in mg/kg/day by the total systemic exposure to hydroxycitronellal, 297/0.013, or 107639.

In addition, the total systemic exposure to hydroxycitronellal (13 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/08/21.

11.1.4. Skin sensitization

Based on the existing data, hydroxycitronellal is a sensitizer with a defined NESIL of 4900 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, hydroxycitronellal is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree v3.0.1; OECD Toolbox v4.2). Hydroxycitronellal was found to be positive in *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens test, and human cell line activation test (h-CLAT) (Natsch et al., 2013; Otsubo et al., 2017). In murine local lymph node assays (LLNAs), hydroxycitronellal was found to be sensitizing with EC3 values ranging from 2300 μg/cm^2 to 12225 μg/cm^2 (RIFM, 2007b; RIFM, 2006c; Basketter and Scholes, 1992; Montelius et al., 1994; RIFM, 2001a; RIFM, 2001b; RIFM, 2001c; RIFM, 2001d; Basketter et al., 2001; Basketter et al., 2002; Basketter et al., 2003; Gerberick et al., 2004; Lalko et al., 2004; Patlewicz et al., 2003; Roberts et al., 2007; RIFM, 2007a; RIFM, 2006b; Piccotti et al., 2007; RIFM, 2006d). In guinea pig maximization tests and Buehler tests with hydroxycitronellal, both positive and negative results were observed (Marzulli and Maguire, 1982; Klecak et al., 1977; RIFM, 1987). Reactions indicative of sensitization were observed in a Confirmation of Induction in Humans test (CNIH) studies when 5814 μg/cm^2 in ethanol or 7752 μg/cm^2 in ethanol was used for induction and challenge applications (RIFM, 1965; RIFM, 1964). However, in a CNIH with 4960 μg/cm^2 of hydroxycitronellal in 1:3 ethanol: diethyl phthalate, no reactions indicative of sensitization was observed in any of the 100 volunteers (RIFM, 2006a).

Based on weight of evidence (WoE) from the available data, hydroxycitronellal is a weak sensitizer with a WoE NESIL of 4900 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 0.99 mg/kg/day.

Additional References: Marzulli and Maguire, 1982; Maisey and Miller, 1986; RIFM, 1962; Klecak et al., 1977; Gad et al., 1986; Klecak (1979); Ishihara et al., 1986; Wahlkvist et al., 1999; Klecak (1985); RIFM, 1975; RIFM, 1976; RIFM, 1977.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hydroxycitronellal 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 hydroxycitronellal in experimental models. 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 et al., 2009). Based on the lack of absorbance, hydroxycitronellal 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 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.

Table 1
Data Summary for hydroxycitronellal.

LLNA Weighted Mean EC3 Value (μg/cm^2) [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
5553 [18][d]	Weak	4960	3450	5814	4900

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.
[d] Only EC3 values from LLNAs with reported; SIs were weighted.

Literature Search and Risk Assessment Completed On: 02/18/21.

11.1.6. Local Respiratory Toxicity

The MOE for hydroxycitronellal is adequate for the respiratory 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, nose-only inhalation study conducted in rats, a NOAEC of 70 mg/m^3 was reported for hydroxycitronellal (RIFM, 2013). The target exposure concentrations were 0.70, 7.0, and 70 mg/m^3, and the overall mean exposure concentrations were 0.84, 6.4, and 73 mg/m^3. Clinical observations were recorded prior to, during, and post-exposure. At necropsy, bronchoalveolar lavage was performed for cytokine analysis, and lung tissue was collected for histopathology (5 animals/sex/group). Additionally, hematology and serum chemistry were considered (5 animals/sex/group). All parameters examined and measured were unaffected by material exposure; however, there was an accumulation of yellow material on the body surface of females in the highest concentration group (70 mg/m^3). This was considered a non-adverse clinical observation. Therefore, the NOAEC was determined to be 70 mg/m^3, the highest exposure concentration tested.

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

- (70 mg/m^3) × (1 m^3/1000 L) = 0.070 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/day
- (0.070 mg/L) × (61.2 L/d) = 4.28 mg/day
- (4.28 mg/day)/(0.0016 kg lung weight of rat*) = 2675 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.081 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (RIFM, 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 et al., 2009) to give 0.12 mg/kg lung weight/day resulting in a MOE of 22291.7 (i.e., [2675 mg/kg lung weight/day]/[0.12 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.081 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): RIFM, 2003b: RIFM, 2002: RIFM, 2003c: Isola and Rogers, 2002: Rogers et al., 2003a: RIFM, 2003d: RIFM, 2003a: RIFM, 2004a: RIFM, 2004b: RIFM, 2004c: Isola et al., 2004a: Rogers et al., 2005: RIFM, 1972: Vethanayagam et al., 2013: RIFM, 2014a.

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 hydroxycitronellal 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 (VoU) Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. However, since the VoU and PEC are proprietary, RIFM cannot include the exact values in the safety assessment. Following the RIFM Environmental Framework, hydroxycitronellal 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 hydroxycitronellal 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 ≥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), hydroxycitronellal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies.

Biodegradation

RIFM, 1990c: A 28-day biodegradation study according to the OECD 301F method was conducted with hydroxycitronellal. Mean biodegradation of 81% was observed after 21 days.

RIFM, 1990a: A biodegradation study was conducted using activated sludge. 30 mg/L of activated sludge was mixed with 40 mg/L of hydroxycitronellal and incubated for 19 days at 20 °C. Dissolved organic carbon was measured. Hydroxycitronellal underwent 99.8% biodegradation in 19 days.

RIFM, 1994: A 28-day biodegradation study using the sealed vessel test according to the OECD 301B method was conducted with 10 mg/L of the test material. Hydroxycitronellal underwent 93.7% biodegradation in 28 days.

RIFM, 1989a: The ready biodegradability of the test material was determined using the respirometric method (modified MITI test) according to the OECD 301C method. Hydroxycitronellal underwent 63.0% biodegradation in 28 days.

RIFM, 2000: The ready biodegradability of the test material was evaluated using the modified MITI test according to the OECD 301C guideline. Biodegradation of 1.1% (BOD) was observed after 28 days.

RIFM, 2019b: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 82% was observed after 28 days.

Ecotoxicity

RIFM, 1989b: A 48-h *Daphnia magna* acute toxicity test was conducted according to the EU Directive 79/831/EEC (4) C2 method under static conditions. The EC50 value based on nominal concentration was reported to be 410 mg/L.

RIFM, 1989c: A fish (*Golden Orfe*) acute toxicity test was conducted with test material according to the DIN 38 412 method under static conditions. The 96-h LC50 value based on nominal concentration was reported to be greater than 21.5 mg/L but less than 46 mg/L.

RIFM, 1989d; **RIFM, 1990b**: Two algae acute toxicity tests were conducted with hydroxycitronellal. In the first test, the 72 h EC50 was reported to be 68 mg/L, while EbC50 of 63.67 mg/L and ErC50 of 123.32 mg/L were reported in the second test.

Other available data

Hydroxycitronellal has been registered under REACH with no additional data available.

Risk assessment refinement

Since hydroxycitronellal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	186.4			1000000	0.1864	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	8.586	13.095	20.501	10000	0.8586	Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	111.911	64.213	49.951			Neutral Organic SAR

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	2.11	2.11
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.8586 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: 03/08/21.

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 10/08/21.

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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112983.

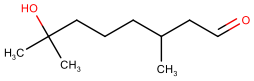
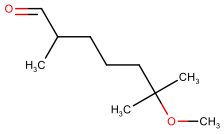
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). 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, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), 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, 2018).
- 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	Hydroxycitronellal	6-Methoxy-2,6-dimethylheptan-1-al
CAS No.	107-75-5	62439-41-2
Structure		
Similarity (Tanimoto Score)		0.73
Endpoint		Genotoxicity
Molecular Formula	$C_{10}H_{20}O_2$	$C_{10}H_{20}O_2$
Molecular Weight	172.268	172.268
Melting Point (°C, EPI Suite)	23.36	−6.46
Boiling Point (°C, EPI Suite)	241.00	205.16
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.73E-01	3.72E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.04E+03	6.24E+02
Log KOW	2.11	2.32
J_{max} (μg/cm^2/h, SAM)	45.87	13.14
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.42E-03	5.85E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	Simple aldehyde	Simple aldehyde
***In Vivo* Mutagenicity (Micronucleus, ISS)**	Simple aldehyde	Simple aldehyde
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on hydroxycitronellal (CAS # 107-75-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 6-Methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2) was used as a read-across analog for the target material hydroxycitronellal (CAS # 107-75-5) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aldehydes.
  - o The target material and the read-across analog share a common aliphatic branched aldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the target has an additional alcohol fragment in the structure while the read-across analog has an additional ether functional group in the structure. The tertiary alcohol on the target material is predicted to undergo conjugation and helps in the excretion of the target material faster compared to the read-across analog.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by an aliphatic branched aldehyde fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog and target material are predicted to have DNA binding alerts by OECD for genotoxicity and carcinogen alerts by ISS and are classified as aldehydes. All the other alerts are negative. Data superseded predictions in this case.
  - 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 endpoints evaluated 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 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.
Q5 Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6 Benzene derivative with certain substituents? No.
Q7 Heterocyclic? No.
Q16 Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17 Readily hydrolyzed to a common terpene? No.
Q19 Open chain? No.
Q20 Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes.
Q21 Three or more different functional groups? No.
Q18 One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). No. Class I (Class Low).

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