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RIFM fragrance ingredient safety assessment, tetrahydrolinalyl acetate, CAS Registry Number 20780-48-7

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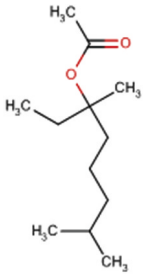


Name: Tetrahydrolinalyl acetate
CAS Registry Number: 20780-48-7
Additional CAS Numbers*:
68480-08-0 (2,6-Dimethyl-2-octyl acetate)
*Included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
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

(*continued on next column*)

(*continued*)

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.

Tetrahydrolinalyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from tetrahydrolinalyl acetate and additional material 2,6-dimethyl-2-octyl acetate (CAS # 68480-08-0) show that tetrahydrolinalyl acetate is not genotoxic. Data on read-across material 2,6-dimethylheptan-2-ol (CAS # 13254-34-7) provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across materials 2,6-dimethylheptan-2-ol (CAS # 13254-34-7) and acetic acid (CAS # 64-19-7) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data show that there are no safety concerns for tetrahydrolinalyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV/Vis spectra; tetrahydrolinalyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; tetrahydrolinalyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2003a; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 76 mg/kg/day.	RIFM (2015)
Reproductive Toxicity: NOAEL = 714 mg/kg/day.	RIFM (2015)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: Tetryhydrolinalyl acetate; ECHA, 2018)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1981a; RIFM, 1981b)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 62% (OECD 301F)	RIFM (2003b)
Bioaccumulation: Screening-level: 510.1 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h green algae EC50: 0.355 mg/L	(ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h green algae EC50: 0.355 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0355 μg/L

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

1. Identification

Chemical Name: Tetrahydrolinalyl acetate	Chemical Name: 2,6-Dimethyl-2-octyl acetate
CAS Registry Number: 20780-48-7	**CAS Registry Number:** 68480-08-0
Synonyms: 3,7-Dimethyloctan-3-yl acetate; 3-Octanol, 3,7-dimethyl-, acetate; Tetrahydro Mugyl Acetate; 酢酸アルキル(C = 7 ~ 2 0)エステル; 1-Ethyl-1,5-dimethylhexyl acetate; Tetrahydrolinalyl acetate	**Synonyms:** 2-Octanol, 2,6-dimethyl-, acetate
Molecular Formula: $C_{12}H_{24}O_2$	**Molecular Formula:** $C_{12}H_{24}O_2$
Molecular Weight: 200.32	**Molecular Weight:** 200.32
RIFM Number: 561	**RIFM Number:** 5914
Stereochemistry: Isomer not specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

CAS # 20780-48-7	CAS # 68480-08-0
Boiling Point: 218.36 °C (EPI Suite)	**Boiling Point:** 218.36 °C (EPI Suite)
Flash Point: 80 °C (Globally Harmonized System), 176 °F; CC (Fragrance Materials Association [FMA]), 75 °C (Givaudan Specification Sheet, 1983)	**Flash Point:** Not available
Log K_{ow}: Log Pow = 5.4 (RIFM, 2003c), 4.61 (EPI Suite)	**Log K_{ow}:** 4.61 (EPI Suite)
Melting Point: -2.29 °C (EPI Suite)	**Melting Point:** -2.29 °C (EPI Suite)
Water Solubility: 5.056 mg/L (EPI Suite)	**Water Solubility:** 5.056 mg/L (EPI Suite)
Specific Gravity: 0.863–0.867 (Givaudan Specification Sheet, 1983)	**Specific Gravity:** Not available
Vapor Pressure: 0.0942 mm Hg at 20 °C (EPI Suite v4.0), 0.06 mm Hg at 20 °C (FMA), 0.143 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.0942 mm Hg at 20 °C (EPI Suite v4.0), 0.143 mm Hg at 25 °C (EPI Suite)
UV Spectra: No significant absorbance between 290 and 400 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: Colorless oily liquid. Practically insoluble in water; soluble in alcohol and oils. Refreshing, citrusy-herbaceous, mildly floral odor of moderate tenacity (Arctander, 1969).	**Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 1.30% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.0078 mg/kg/day or 0.57 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.030 mg/kg/day (RIFM, 2016)

*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 IV. 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).

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	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. Analogs Selected

a. **Genotoxicity:** 2,6-Dimethyl-2-octyl acetate (CAS # 68480-08-0)
b. **Repeated Dose Toxicity:** 2,6-Dimethylheptan-2-ol (CAS # 13254-34-7)
c. **Reproductive Toxicity:** 2,6-Dimethylheptan-2-ol (CAS # 13254-34-7) and acetic acid (CAS # 64-19-7)
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

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

8. NAatural occurrence

Tetrahydrolinalyl acetate is not reported to occur in foods by the VCF*.

2,6-Dimethyl-2-octyl acetate is not reported to occur in foods by the VCF.

*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 for tetrahydrolinalyl acetate (20780-48-7); accessed on 09/29/21 (ECHA, 2018). 2,6-Dimethyl-2-octyl acetate (68480-08-0) has been pre-registered for 2010; no dossier available as of 10/06/21.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of tetrahydrolinalyl acetate 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 and preincubation

methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with tetrahydrolinalyl acetate 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 concentration in the presence or absence of S9 (RIFM, 2003a). Under the conditions of the study, tetrahydrolinalyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of tetrahydrolinalyl acetate. The clastogenic activity of additional material 2,6-dimethyl-2-octyl acetate (CAS # 68480-08-0) 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 2,6-dimethyl-2-octyl acetate in DMSO at concentrations up to 200 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h 2,6-Dimethyl-2-octyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, 2,6-dimethyl-2-octyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to tetrahydrolinalyl acetate.

Based on the available data, 2,6-dimethyl-2-octyl acetate does not present a concern for genotoxic potential, and this can be extended to tetrahydrolinalyl acetate.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for tetrahydrolinalyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on tetrahydrolinalyl acetate. Read-across material 2,6-dimethylheptan-2-ol (CAS # 13254-34-7; see Section VI) has sufficient repeated dose toxicity data that can be used to support the repeated dose toxicity endpoint. An OECD 422/GLP-compliant combined repeated dose and reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing 2,6-dimethylheptan-2-ol (Dimetol) at doses of 0, 1000, 3000, or 10000 ppm. Males were exposed for 29 days (2 weeks prior to mating, during mating, and up to termination), while females were exposed for 39–57 days (2 weeks prior to mating, during mating, during post-coitum, and up to day 4 of lactation). At 10000 ppm, the bodyweight gain for males was statistically significantly decreased from day 8 of the premating period onwards, which was likely due to the palatability of the test material, as food consumption was also decreased in the first week of treatment. The absolute liver weights were increased among males (not significant) and females (statistically significant) in the highest dose group. The relative liver weights were statistically significantly increased among males and females in the highest dose group. The relative liver weights were 16% and 20% higher for males and females, respectively, as compared to the controls. Microscopic evaluation revealed accumulation of cortical hyaline droplets representing α-2u-globulin at an increased incidence and severity in the kidneys of males treated at 10000 ppm, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). Tubular basophilia was also present at an increased incidence and severity, and in 1 instance, granular casts were observed among males of the highest dose group. These granular casts were considered to be indicative of primary tubular injury; therefore, this finding was considered to be adverse. Since there was no histopathological or clinical chemistry evidence of liver degeneration or necrosis, the liver weight increases were considered to be adaptive (Hall, 2012). The NOAEL for repeated dose toxicity was considered to be 3000 ppm (228–231 mg/kg/day for males and 251–382 mg/kg/day for females, when corrected for the mean daily intake), based on a decrease in bodyweight gain and alterations in the kidney among animals of the highest dose group (RIFM, 2015; ECHA, 2017b). The most conservative NOAEL of 228 mg/kg/day was considered for the repeated dose toxicity endpoint.

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*.

The derived NOAEL for the repeated dose toxicity data is 228/3 or 76 mg/kg/day.

The tetrahydrolinalyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,6-dimethylheptan-2-ol NOAEL in mg/kg/day by the total systemic exposure to tetrahydrolinalyl acetate, 76/0.030, or 2533.

*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: 11/25/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on tetrahydrolinalyl acetate. Read-across material 2,6-dimethylheptan-2-ol (CAS # 13254-34-7; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. Acetic acid has been reviewed by EFSA (EFSA, 2012), NICNAS (NICNAS, 2013), and JECFA (WHO, 2006) for its use as a food additive and by CIR (CIR (1994) for its use in cosmetics. It was concluded that acetic acid does not show specific reproductive or developmental toxicity. Acetic acid is recognized as Generally Recognized as Safe (GRAS) by the US FDA and is estimated to be consumed by humans at about 1 gm/day for centuries without any adverse effects. Furthermore, estimations of the daily intake of acetic acid have also been reported to vary from about 1 to 2.1 g per day for subjects older than 2 years (NICNAS, 2013).

An OECD 422/GLP-compliant combined repeated dose and reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing 2,6-dimethylheptan-2-ol (Dimetol) at doses of 0, 1000, 3000, or 10000 ppm. Males were exposed for 29 days (2 weeks prior to mating, during mating, and up to termination), while females were exposed for 39–57 days (2 weeks prior to mating, during mating, during post-coitum, and up to day 4 of lactation). In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. One control and 1 low-dose female were euthanized before their scheduled necropsies after having total litter losses. Early resorption in the right uterine horn was observed for the control female with a total litter loss. Both females had only 1 pup, which was determined not to be treatment-related. There were no treatment-related adverse effects on mating, fertility and conception indices, pre-coital time, number of corpora lutea and implantation sites, gestation index, parturition, maternal care, or early postnatal pup development. There were 2, 3, and 3 pups that died/went missing during the first days of lactation in the control, 1000, and 10000 ppm groups, respectively. There were no pups lost at 3000 ppm. Missing pups were most likely cannibalized. No toxicological relevance was attributed to these dead/missing pups since the mortality incidence did not show a dose-related trend and was within the range considered normal for pups of this age. No other treatment-related findings were observed in

postnatal loss, viability index, sex ratio, clinical signs, bodyweight development, or macroscopic examination of pups. The NOAEL for fertility and developmental toxicity was considered to be 10000 ppm (714–734 mg/kg/day for males and 830–1216 mg/kg/day for females, when corrected for the mean daily intake), the highest dose tested (RIFM, 2015; also available in ECHA, 2017b). The most conservative NOAEL of 714 mg/kg/day was considered for the reproductive toxicity endpoint.

Therefore, the tetrahydrolinalyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the 2,6-dimethylheptan-2-ol NOAEL in mg/kg/day by the total systemic exposure to tetrahydrolinalyl acetate, 714/0.030, or 23800. There are insufficient reproductive toxicity data on tetrahydrolinalyl acetate. Read-across materials 2,6-dimethylheptan-2-ol (CAS # 13254-34-7) and acetic acid (CAS # 64-19-7; see Section VI) have sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. Acetic acid has been reviewed by EFSA (EFSA, 2012), NICNAS (NICNAS, 2013), and JECFA (WHO, 2006) for its use as a food additive and by CIR, 1994 for its use in cosmetics. It was concluded that acetic acid does not show specific reproductive or developmental toxicity. Acetic acid is recognized as GRAS by the US FDA and is estimated to be consumed by humans at about 1 gm/day for centuries without any adverse effects. Furthermore, estimations of the daily intake of acetic acid have also been reported to vary from about 1 to 2.1 g per day for subjects older than 2 years (NICNAS, 2013).

Therefore, the tetrahydrolinalyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the 2,6-dimethylheptan-2-ol NOAEL in mg/kg/day by the total systemic exposure to tetrahydrolinalyl acetate, 714/0.030, or 23800.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data, tetrahydrolinalyl acetate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, tetrahydrolinalyl acetate is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Tetrahydrolinalyl acetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and a KeratinoSens but positive in a U937-CD86 test (ECHA, 2018). In a murine local lymph node assay (LLNA), tetrahydrolinalyl acetate was found to be non-sensitizing when tested up to 5% (1250 μg/cm^2) (ECHA, 2018). In guinea pigs, an open epicutaneous test (OET) and a Freund's complete adjuvant test (FCAT) with tetrahydrolinalyl acetate did not present reactions indicative of sensitization at 100% and 5%, respectively (RIFM, 1981c; RIFM, 1981d). In a human maximization test, no skin sensitization reactions were observed with tetrahydrolinalyl acetate at 4% (2760 μg/cm^2) (RIFM, 1974). In Confirmation of No Induction in Humans tests (CNIHs) conducted at 6.25% (4845 μg/cm^2) of tetrahydrolinalyl acetate in alcohol and 2% (no patch size reported) in dimethyl phthalate, no reactions indicative of sensitization were observed in any of the 41 and 54 volunteers, respectively (RIFM, 1965; RIFM, 1970).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, as well as animal and human studies, tetrahydrolinalyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/21/20.

11.1.5. Phototoxicity/Photoallergenicity

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

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In guinea pig phototoxicity and photoallergenicity studies, there was no evidence of phototoxic reactions to exposure to 30% tetrahydrolinalyl acetate (RIFM, 1981b) or photoallergic responses to 10% tetrahydrolinalyl acetate in alcohol (RIFM, 1981a). Based on the lack of absorbance and the available *in vivo* study data, tetrahydrolinalyl acetate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for tetrahydrolinalyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on tetrahydrolinalyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.57 mg/day. This exposure is 2.46 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydrolinalyl acetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{ow}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, tetrahydrolinalyl acetate 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 tetrahydrolinalyl acetate 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, 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), tetrahydrolinalyl acetate 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 # 20780-48-7.

RIFM, 2003b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Biodegradation of 62% was observed after 28 days.

Ecotoxicity: No data available.

11.2.2.1.2. Other available data. Tetrahydrolinalyl acetate (CAS # 20780-48-7) has been registered under REACH with the following additional data available (ECHA, 2018):

A ready biodegradation study was conducted according to the OECD 301F method. Biodegradation of 55% was observed after 28 days.

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on mean measured concentration was reported to be greater than 0.09 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The test material is low water-soluble, and a supersaturated stock with a loading rate of 100 mg/L was made. The 48-h ErL50 based on nominal test concentration was reported to be greater than 100 mg/L.

11.2.2.1.3. Risk assessment refinement. Since tetrahydrolinalyl acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.4	5.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

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

The RIFM PNEC is 0.0355 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 volumes of use.

Literature Search and Risk Assessment Completed On: 12/11/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.2971			1000000	0.0002971	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.803	1.262	0.355	10000	0.0355	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.748	0.540	1.089			Neutral Organics

- **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 09/31/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112871.

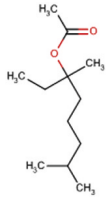
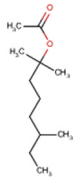
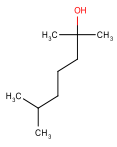
Appendix

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, 2017a).

- 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 Materials		
Principal Name	Tetrahydrolinalyl acetate	2,6-Dimethyl-2-octyl acetate	2,6-Dimethyl-2-heptanol	Acetic acid
CAS No.	**20780–48–7** (68480-08-0)	68480-08-0	13254-34-7	64-19-7
Structure				
Similarity (Tanimoto Score)		0.92	N/A	N/A
Read-across Endpoint		• Genotoxicity	• Repeated dose toxicity • Reproductive toxicity	• Reproductive toxicity
Molecular Formula	$C_{12}H_{24}O_2$	$C_{12}H_{24}O_2$	$C_9H_{20}O$	$C_2H_4O_2$
Molecular Weight	200.32	200.32	144.26	60.05

(*continued on next page*)

(*continued*)

	Target Material	Read-across Materials		
Principal Name	Tetrahydrolinalyl acetate	2,6-Dimethyl-2-octyl acetate	2,6-Dimethyl-2-heptanol	Acetic acid
Melting Point (°C, EPI Suite)	−2.29	−2.29	−23.45	16
Boiling Point (°C, EPI Suite)	218.36	218.36	172.11	118
Vapor Pressure (Pa @ 25°C, EPI Suite)	19	19	48.5	12.9
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.61	4.61	3.11	0.09
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.056	5.056	572	475900
J_{max} (mg/cm^2/h, SAM)	23.658	19.095	147.341	6283.04
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.28E+002	2.28E+002	4.17E+000	5.477E-007
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2- Schiff base formation after aldehyde release • SN1- Nucleophilic attack after carbenium ion formation	• AN2- Schiff base formation after aldehyde release • SN1- Nucleophilic attack after carbenium ion formation		
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found		
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	• Acetamide (Renal Toxicity) Alert/ Carboxylic acids (Hepatotoxicity) No rank
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)		• Non-toxicant (low reliability)	• Toxicant (low reliability)
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	N/A	N/A

N/A: Not applicable. The substances are metabolites of the target material.

Summary

There are insufficient toxicity data on tetrahydrolinalyl acetate (CAS # 20780-48-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2,6-dimethyl-2-octyl acetate (CAS # 68480-08-0), 2,6-dimethyl-2-heptanol (CAS # 13254-34-7), and acetic acid (CAS # 64-19-7) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target material tetrahydrolinalyl acetate (CAS # 20780-48-7) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to tetrahydrolinool (CAS # 78-69-3) and acetic acid (CAS # 64-19-7) in the first step with a 0.95 probability. 2,6-Dimethyl-2-heptanol (CAS # 13254-34-7) is structurally similar to the target metabolite tetrahydrolinalyl acetate. Hence, 2,6-dimethyl-2-heptanol (CAS # 13254-34-7) and acetic acid (CAS # 64-19-7) can be used as read-across for the target material. Read-across 2,6-dimethyl-2-heptanol (CAS # 13254-34-7) was out of the domain for the *in vivo* rat and out of the domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

Conclusions

- 2,6-Dimethyl-2-octyl acetate (CAS # 68480-08-0) was used as a read-across analog for the target material tetrahydrolinalyl acetate (CAS # 20780-48-7) for the genotoxicity endpoint. The read-across analog is one of the 2 isomeric materials evaluated in this safety assessment, but the availability of relevant data for the genotoxicity endpoint enables its use as a read-across analog.
  - o The target material and the read-across analog are structurally similar and belong to the class of saturated aliphatic esters.
  - o The target material and the read-across analog differ by the position of 1 methyl group in the branched alkyl structure and by the presence of an ethyl versus a methyl group on the α carbon. These structural differences are toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. 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.

- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material, as well as the read-across analog, are predicted to be Schiff base formers by the DNA binding model within OECD QSAR Toolbox. The data described in the genotoxicity section confirm that the read-across analog does not pose a concern for genetic toxicity. Based on the structural similarity between the target material and the read-across analog, and data for read-across analog, the prediction is superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 2,6-Dimethyl-2-heptanol (CAS # 13254-34-7) was used as a read-across analog for the target material tetrahydrolinalyl acetate (CAS # 20780-48-7) for the repeated dose toxicity and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - The key structural differences between the target material and the read-across analog are that they share different branching in the saturated aliphatic fragment. Also, this structural difference can be mitigated by the fact that the read-across analog is structurally similar to the major metabolite of the target material. These structural differences between the read-across analog and the target and its metabolites are toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The read-across material acetic acid (CAS # 64-19-7) has an alert of Acetamide precursor Renal Toxicity alert and Carboxylic acids Hepatotoxicity alert with no rank under HESS categorization. The wealth of data in the literature suggests fast rates of clearance for acetic acid. Also, acetic acid is one of the natural constituents of the human metabolome according to the human metabolome database. Therefore, the alerts for acetic acid are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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