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RIFM fragrance ingredient safety assessment, 2,6-dimethyl-2-heptanol, CAS Registry Number 13254-34-7

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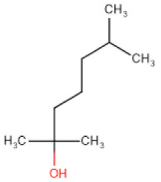
CAS Registry Number: 13254-34-7



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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., 2021)

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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.

2,6-Dimethyl-2-heptanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2,6-dimethyl-2-heptanol is not genotoxic. Data on 2,6-dimethyl-2-heptanol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog tetrahydrolinalool (CAS # 78-69-3) provided 2,6-dimethyl-2-heptanol a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; 2,6-dimethyl-2-heptanol is not phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2,6-dimethyl-2-heptanol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2,6-dimethyl-2-heptanol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2002; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 238 mg/kg/day.	RIFM (2015a)
Reproductive Toxicity: Developmental toxicity and Fertility: NOAEL = 714 mg/kg/day.	RIFM (2015a)
Skin Sensitization: NESIL = 11000 μg/cm^2.	RIFM (2021)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra; RIFM Database; RIFM, 1983; RIFM, 1981a; RIFM, 1981b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence Critical Measured Value: 75% (OECD 301F)	RIFM (1998)
Bioaccumulation: Screening-level: 52. L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 7.481 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: 48-h *Daphnia magna* LC50: 7.481 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.7481 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1	

1. Identification

1. **Chemical Name:** 2,6-Dimethyl-2-heptanol
2. **CAS Registry Number:** 13254-34-7
3. **Synonyms:** Dimetol; Freesiol; 2-Heptanol, 2-6-dimethyl-; Lolitol; アルカノール(C = 5 ~ 38); 2,6-Dimethylheptan-2-ol; 2,6-Dimethyl-2-heptanol
4. **Molecular Formula:** $C_9H_{20}O$
5. **Molecular Weight:** 144.25 g/mol
6. **RIFM Number:** 833
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 172.11 °C (EPI Suite), 177 °C (450 K) at 1010 ± 1 hPa (RIFM, 2014)
2. **Flash Point:** 63 °C (Globally Harmonized System), 145 °F; CC (Fragrance Materials Association [FMA]), 68 °C (RIFM, 2014)
3. **Log K_{OW}:** 3.0 at 45 °C (RIFM, 1996a), 3.0 at 45 °C (RIFM, 1996b), 3.11 (EPI Suite)
4. **Melting Point**: -23.45 °C (EPI Suite), less than −80 °C (<193 K) (RIFM, 2014)
5. **Water Solubility:** 572 mg/L (EPI Suite)
6. **Specific Gravity:** 0.8135 (RIFM), 0.811 (FMA)
7. **Vapor Pressure:** 0.237 mm Hg at 20 °C (EPI Suite v4.0), 0.2 mm Hg 20 °C (FMA), 0.364 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a fresh, woody, floral odor

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 v3.1.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.25% (RIFM, 2020a)
2. **Inhalation Exposure*:** 0.00047 mg/kg/day or 0.036 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.0050 mg/kg/day (RIFM, 2020a)

*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).

5. Derivation of systemic absorption

1. **Dermal:** 100%

RIFM, 1984: The dermal penetration of 2,6-dimethyl-2-heptanol in an *in vitro* system utilizing the excised skin of naked rat and pig was determined under unoccluded conditions. The test material, a mixture of 14C labeled and non-radioactive material dissolved in ethanol at a concentration of 30%, was applied to a skin area of 5 cm^2 at a dose of 6 µL/cm^2 (1800 µg active substance/cm^2). The specific activity used for labeling was 345.37 µCi/mL. Absorption was evaluated at 1, 6, and 16 h after application. Radioactivity was measured in skin washings (residual material), stratum corneum, skin strippings (horny layer), and receptor fluid. The test material penetrated into and through the rat and pig skin. The total skin absorption values were time- and species-dependent. On naked rat skin, the total absorption values (amount in the horny layer from tape strippings, amount in the remaining skin, and amount in the chamber liquid combined) after 1 and 16 h were 300 and 900 µg/cm^2, respectively. On pigskin the total skin absorption values 23 and 104 µg/cm^2 after 1 and 16 h of exposure, respectively. This was significantly lower than the rat. Due to the high volatility of the test material, it was assumed that approximately 40%–60% of the test material was lost due to evaporation from the skin. For the naked rat after 16 h of exposure, 1.4% of the applied dose was in the horny layer (tape strippings) and 33.2% was in the remaining skin tissue layers. The amount of test material found in the chamber liquid was 14.6% of the total applied dose. The residual material on the skin surface was 5.8%. Thus, it was concluded that 49.2% of 2,6-dimethyl-2-heptanol was absorbed by naked rat skin. The total recovery accounted for was 55%. For the pig after 16 h of exposure, 0.4% of the applied dose was in the horny layer, and 4.0% was in the remaining skin tissue layers. The amount of test material found in the chamber liquid was 1.4% of the total applied dose. The residual material on the skin surface was 16.3%. Thus, it was concluded that 5.8% of 2,6-dimethyl-2-heptanol was absorbed by pig skin. The total recovery accounted for was only 22.1%. Since there was significant evaporative loss and the amount of test material recovered during the experiment was significantly low (rats 55% and pigs 22.1%), the study results were unable to determine total skin absorption values. Therefore, the skin absorption value was conservatively determined to be 100%.

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	III

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Tetrahydrolinalool (CAS # 78-69-3)
   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

2,6-Dimethyl-2-heptanol 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; accessed 05/10/21 (ECHA, 2017a).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,6-dimethyl-2-heptanol 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)	0.012
2	Products applied to the axillae	0.25
3	Products applied to the face/body using fingertips	1.9
4	Products related to fine fragrances	4.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.2
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	1.2
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.2
5D	Baby cream, oil, talc	0.40
6	Products with oral and lip exposure	0.37
7	Products applied to the hair with some hand contact	1.5
8		0.40

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Products with significant ano-genital exposure (tampon)	
9	Products with body and hand exposure, primarily rinse-off (bar soap)	9.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	11
10B	Aerosol air freshener	13
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.40
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 2,6-dimethyl-2-heptanol, the basis was the subchronic reference dose of 2.38 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 11000 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, 2,6-dimethyl-2-heptanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2,6-dimethyl-2-heptanol 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 2,6-dimethyl-2-heptanol 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, 2002). Under the conditions of the study, 2,6-dimethyl-2-heptanol was not mutagenic in the Ames test.

The clastogenic activity of 2,6-dimethyl-2-heptanol 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-heptanol in DMSO at concentrations up to 1442 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 430 μg/mL in the presence and absence of metabolic activation. 2,6-Dimethyl-2-heptanol did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2015b). Under the conditions of the study, 2,6-dimethyl-2-heptanol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2,6-dimethyl-2-heptanol does not present a concern for genotoxic potential.

Additional References: RIFM, 2001; RIFM, 2013.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for 2,6-dimethyl-2-heptanol 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 2,6-dimethyl-2-heptanol. In a GLP and OECD 422-compliant study, 10 SPF-bred Wistar Han rats/sex/dose were administered 2,6-dimethyl-2-heptanol via the diet at doses of 0, 1000, 3000, and 10000 ppm (corresponding to 0, 70, 228, and 714 mg/kg/day for males and 0, 80, 251, and 830 mg/kg/day for females, according to the study report). Males were treated for 29 days (2 weeks prior to mating, during mating, and up to termination); females were treated for 39–57 days (during 2 weeks prior to mating, during mating, during postcoitum, and during at least 4 days of lactation). No mortality occurred throughout the treatment period. No treatment-related effects were seen in clinical appearance, functional observations, clinical laboratory investigations, or macroscopic examination. Bodyweight gains were decreased in males at the high dose, but this was attributed to palatability issues. Cortical hyaline droplets were detected with increased incidence and severity in the kidneys of males at the high dose, but this was attributed to α-2u-globulin nephropathy (immunohistochemistry not mentioned). α-2u-Globulin nephropathy is specific to male rats and thus not considered relevant to human health. Absolute and relative liver weights were increased in both sexes at the high dose; however, there were no accompanying histopathological effects. In the absence of treatment-related adverse effects up to the highest dose, the NOAEL for this study was considered to be 714 mg/kg/day (RIFM, 2015a).

A default safety factor of 3 was used when deriving a NOAEL from the 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 714/3 or 238 mg/kg/day.

Therefore, the 2,6-dimethyl-2-heptanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,6-dimethyl-2-heptanol NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-2-heptanol, 238/0.0050, or 47600.

In addition, the total systemic to 2,6-dimethyl-2-heptanol (5.0 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.

11.1.2.1.1. Derivation of subchronic reference dose (RfD). 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, 2020c) and a subchronic RfD of 2.38 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 2,6-dimethyl-2-heptanol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 238 mg/kg/day by the uncertainty factor, 100 = 2.38 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.3. Reproductive toxicity

The MOE for 2,6-dimethyl-2-heptanol 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 2,6-dimethyl-2-heptanol. In a GLP and OECD 422-compliant study, 10 SPF-bred Wistar Han rats/sex/dose were administered 2,6-dimethyl-2-heptanol via the diet at doses of 0, 1000, 3000, and 10000 ppm (corresponding to 0, 70, 228, and 714 mg/kg/day for males and 0, 80, 251, and 830 mg/kg/day for females, according to the study

report). Males were treated for 29 days (2 weeks prior to mating, during mating, and up to termination); females were treated for 39–57 days (during 2 weeks prior to mating, during mating, during postcoitum, and during at least 4 days of lactation). No mortality occurred throughout the treatment period. No treatment-related adverse effects were observed on mating, fertility and conception indices, precoital time, number of corpora lutea and implantation sites, gestation index and duration, parturition, maternal care, sex ratio, or early postnatal pup development (mortality, clinical signs, body weights, and macroscopic examination). In the absence of treatment-related adverse effects up to the highest dose, the developmental toxicity and fertility NOAEL for this study was considered to be 714 mg/kg/day (RIFM, 2015a).

Therefore, the 2,6-dimethyl-2-heptanol MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the 2,6-dimethyl-2-heptanol NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-2-heptanol, 714/0.0050, or 142800.

In addition, the total systemic to 2,6-dimethyl-2-heptanol (5.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.4. Skin sensitization

Based on the available data and read-across material tetrahydrolinalool (CAS # 78-69-3), 2,6-dimethyl-2-heptanol is considered a skin sensitizer with a defined NESIL of 11000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2,6-dimethyl-2-heptanol. Based on the existing data and read-across material tetrahydrolinalool (CAS # 78-69-3; see Section VI), 2,6-dimethyl-2-heptanol is considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material tetrahydrolinalool was found to be sensitizing with an EC3 value of 7.6% (1900 μg/cm^2) (ECHA, 2011; RIFM, 2017). In human maximization tests, no skin sensitization reactions were observed with 10% (6900 μg/cm^2) and 4% (2760 μg/cm^2) 2,6-dimethyl-2-heptanol and read-across material tetrahydrolinalool, respectively (RIFM, 1976a; RIFM, 1976b). In Confirmation of No Induction in Humans tests (CNIH), no skin sensitization reactions were observed with 2,6-dimethyl-2-heptanol at 2% in dimethyl phthalate (DMP) (patch size not reported) and 3876 μg/cm^2 in SDA 39C in any of the 53 and 10 volunteers, respectively (RIFM, 1969; RIFM, 1972; RIFM, 1971). Additionally, in 2 CNIHs with 27% or 11250 μg/cm^2 and 10% or 4132 μg/cm^2 of read-across material tetrahydrolinalool in 1:3 alcohol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 109 and 110 volunteers, respectively (RIFM, 2021; RIFM, 2020d).

Based on weight of evidence (WoE) from structural analysis, human studies, and data on the read-across material tetrahydrolinalool, 2,6-dimethyl-2-heptanol is a sensitizer with a WoE NESIL of 11000 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, 2020c) and a subchronic RfD of 2.38 mg/kg/day.

Additional References: RIFM, 1982; Watanabe (1988); RIFM, 1970.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.5. Phototoxicity/photoallergenicity

Based on UV absorption spectra and the available data, 2,6-dimethyl-2-heptanol does not present a concern for phototoxicity or photoallergenicity.

Table 1
Data summary for tetrahydrolinalool as read-across material for 2,6-dimethyl-2-heptanol.

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[3] μg/cm^2
1900 [1]	Moderate	11250	2760	NA	11000

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.

11.1.5.1. Risk assessment. The available UV absorption spectrum demonstrates that this material does not absorb in the region of 290–400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a study conducted in human volunteers, no phototoxic response was observed after application of 10% 2,6-dimethyl-2-heptanol and UV exposure (RIFM, 1983). Additionally, no phototoxic or photoallergenic responses were reported in a series of guinea pig studies (RIFM, 1981a; RIFM, 1981b). Based on the available UV spectra and the study data, 2,6-dimethyl-2-heptanol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 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: 06/02/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2,6-dimethyl-2-heptanol 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 2,6-dimethyl-2-heptanol. Based on the Creme RIFM Model, the inhalation exposure is 0.036 mg/day. This exposure is 38.9 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: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6-dimethyl-2-heptanol 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, 2,6-dimethyl-2-heptanol 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 2,6-dimethyl-2-heptanol 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 ≥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), 2,6-dimethyl-2-heptanol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1998:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. After 28 days, biodegradation of 75% was observed under the conditions of the study.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2,6-Dimethyl-2-heptanol has been registered under REACH with the following additional data available at this time (ECHA, 2017a):

The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guideline under static conditions. The 96-h LC50 value based on nominal concentrations was reported to be > 22 and < 46 mg/L. The calculation made by the registrant gives an LC50 of 31.6 mg/L based on nominal concentrations and 23.9 mg/L based on initial measured concentrations.

11.2.3. Risk assessment refinement

Since 2,6-dimethyl-2-heptanol 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	3.0	3.0
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**

Based on available data, the RQ for this material is < 1. Additional assessment is not necessary.

The RIFM PNEC is 0.7481 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: 06/03/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	26.25			1000000	0.02625	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	11.88	7.481	8.519	10000	0.7481	Neutral Organics

- **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 12/10/21.

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.2022.112956.

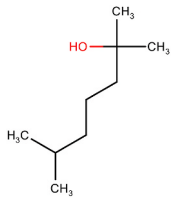
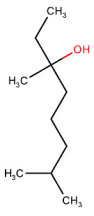
Appendix

Read-across justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020b). 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, 2017b).

- 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	2,6-Dimethyl-2-heptanol	Tetrahydrolinalool
CAS No.	13254-34-7	78-69-3
Structure		
Similarity (Tanimoto Score)		0.96
SMILES	CC(C)CCCC(C)(C)O	CCC(C)(O)CCCC(C)C
Endpoint		Skin sensitization
Molecular Formula	$C_9H_{20}O$	$C_{10}H_{22}O$
Molecular Weight (g/mol)	144.258	158.285

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Melting Point (°C, EPI Suite)	−23.45	31.50
Boiling Point (°C, EPI Suite)	173.00	196.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.85E+01	9.51E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.72E+02	1.89E+02
Log KOW	3.11	3.6
J_{max} (μg/cm^2/h, SAM)	59.55	23.79
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.17E+00	5.54E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.
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 2,6-dimethyl-2-heptanol (CAS # 13254-34-7). Hence *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, tetrahydrolinalool (CAS # 78-69-3) was identified as a read-across analog with sufficient toxicological data.

Conclusions

- Tetrahydrolinalool (CAS # 78-69-3) is used as structurally similar read-across analog for 2,6-dimethyl-2-heptanol (CAS # 13254-34-7) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated branched tertiary alcohols.
  - o The target material and the read-across analog have a branched tertiary alcohol fragment common among them.
  - o The key difference between the target material and the read-across analog is that the target the aliphatic chain length. The target material has a 7-carbon long branched chain while the read-across analog has an 8-carbon long branched chain. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The 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 a comparison of their toxicological properties.
  - o The target material and read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the skin sensitization endpoint are consistent between the read-across analog and the target material.

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia, 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer, 1978).

Q1. Normal constituent of the body **No**
Q2. Contains functional groups associated with enhanced toxicity **No**
Q3. Contains elements other than C,H,O,N,divalent S **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate **No**
Q6. Benzene derivative with certain substituents **No**
Q7. Heterocyclic **No**
Q16. Common terpene **No**
Q17. Readily hydroly zed to a common terpene **No**
Q19. Open chain **Yes**
Q20. Aliphatic with some functional groups **Yes**
Q21. Does the structure contain 3 or more different types of functional groups **No**
Q18. Is substance one of the list (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **No,** Class Low (Class I)

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