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Short Review

RIFM fragrance ingredient safety assessment,1-(2,2,6-trimethylcyclohexyl)-3-hexanol, CAS Registry Number 70788-30-6

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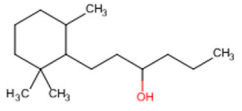
CAS Registry Number: 70788-30-6



Abbreviation/Definition List:

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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)

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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., 2015, 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 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.

1-(2,2,6-Trimethylcyclohexyl)-3-hexanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is not genotoxic and provide a Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data provided 1-(2,2,6-trimethylcyclohexyl)-3-hexanol a No Expected Sensitization Induction Level (NESIL) of 3100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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, 2006; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 66.6 mg/kg/day. (RIFM, 2017e)
Reproductive Toxicity: Developmental toxicity NOAEL = 200 mg/kg/day. Fertility NOAEL = 600 mg/kg/day. (RIFM, 2017e)
Skin Sensitization: NESIL = 3100 μg/cm^2 RIFM (2017d)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM Database; RIFM, 1984)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 50% (OECD 302C) RIFM (2009)
Bioaccumulation: Screening-level: 3113 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 7 day Fish NOEC: 0.22 mg/L RIFM (2005)
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: 7-day Fish NOEC: 0.22 mg/L RIFM (2005)
RIFM PNEC is: 4.4 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** 1-(2,2,6-Trimethylcyclohexyl)-3-hexanol
2. **CAS Registry Number:** 70788-30-6
3. **Synonyms:** Cyclohexanepropanol, 2,2,6-trimethyl-.α.-propyl-; Timberol; 2,2,6-Trimethyl-a-propylcyclohexanepropanol; 1-(2,2,6-トリメチルシクロヘキシル)ヘキサン-3-オール; Norlimbanol Dextro; 1-(Trimethylcyclohexyl)-hexanol; Norlimbanol; Riechstoff Timberol; 1-(2,2,6-Trimethylcyclohexyl)-3-hexanol
4. **Molecular Formula:** $C_{15}H_{30}O$
5. **Molecular Weight:** 226.4
6. **RIFM Number:** 1190
7. **Stereochemistry:** Three stereocenters and a total of 8 isomers possible.

2. Physical data

1. **Boiling Point:** 295.02 °C (EPI Suite)
2. **Flash Point:** 257°F (RIFM Database), 252°F (RIFM Database)
3. **Log K_{OW}:** 5.8 (EPI Suite)
4. **Melting Point**: 56.43 °C (EPI Suite)
5. **Water Solubility:** 1.149 mg/L (EPI Suite)
6. **Specific Gravity:** 0.8947–0.9007 (25 °C) (RIFM Database), 0.896–0.902 (20/4 °C) (RIFM Database), 0.8910–0.9050 (RIFM Database)
7. **Vapor Pressure:** 9.5e-005 mm Hg at 25 °C (EPI Suite), 0.0000462 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})

9. **Appearance/Organoleptic:** A clear, colorless liquid with a strong woody odor

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. 95th Percentile Concentration in Fine Fragrance: 0.62% (RIFM, 2019)
2. Inhalation Exposure*: 0.00039 mg/kg/day or 0.027 mg/day (RIFM, 2019)
3. Total Systemic Exposure**: 0.0054 mg/kg/day (RIFM, 2019)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
a. Genotoxicity: None
b. Repeated Dose Toxicity: None
c. Developmental and Reproductive Toxicity: None
d. Skin Sensitization: None
e. Phototoxicity/Photoallergenicity: None
f. Local Respiratory Toxicity: None
g. Environmental Toxicity: None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

1-(2,2,6-Trimethylcyclohexyl)-3-hexanol is not reported to occur in food 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

Pre-registered for 2010; no dossier available as of 10/08/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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)	0.17
2	Products applied to the axillae	0.071
3	Products applied to the face/body using fingertips	0.51
4	Products related to fine fragrances	1.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.34
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.34
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.34
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.17
7	Products applied to the hair with some hand contact	0.51
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.68
10B	Aerosol air freshener	4.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 1-(2,2,6-trimethylcyclohexyl)-3-hexanol, the basis was a reference dose of 0.67 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 3100 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).
cCalculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. 1-(2,2,6-trimethylcyclohexyl)-3-hexanol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and

without metabolic activation (RIFM, 2015b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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 TA102 were treated with 1-(2,2,6-trimethylcyclohexyl)-3-hexanol in solvent 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, 2006). Under the conditions of the study, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol was not mutagenic in the Ames test.

The clastogenic activity of 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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 1-(2,2,6-trimethylcyclohexyl)-3-hexanol in DMSO at concentrations up to 150 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h 1-(2,2,6-Trimethylcyclohexyl)-3-hexanol 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, 2015a). Under the conditions of the study, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol does not present a concern for genotoxic potential.

Additional References: RIFM, 1985a; RIFM, 2016a; RIFM, 2016b.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

The MOE for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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 1-(2,2,6-trimethylcyclohexyl)-3-hexanol. In an OECD TG 422 and GLP-compliant combined repeated dose toxicity study with a reproduction/development toxicity screening test, 12 Sprague Dawley Crl:CD rats/sex/dose were treated with 1-(2,2,6-trimethylcyclohexyl)-3-hexanol via gavage at doses of 0 (vehicle: corn oil), 60, 200, and 600 mg/kg/day. Males were treated once daily for 49 days (2 weeks prior to mating, during 2 weeks of mating, and 21 days of post-mating) before necropsy. Females were treated once daily for 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. Additionally, 6 animals/sex/dose were included as recovery groups at 0 and 600 mg/kg/day for an additional 14 days. No treatment-related mortality was reported at any dose level. Clinical signs such as mucous stools (15/24) were reported in both sexes at 600 mg/kg/day of the main group. Additionally, mucous stools (10/12) were observed in both sexes of the 600 mg/kg/day recovery group. Mucous stools were considered an adverse effect. No treatment-related adverse effects were reported for body weight, food consumption, hematology, clinical chemistry, urinalysis, necropsy, organ weights, neuropathology findings, or histopathology at any dose level. Based on mucous stools reported at 600 mg/kg/day, the NOAEL for repeated dose toxicity was considered to be 200 mg/kg/day (RIFM, 2017e).

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*.

Thus, the derived NOAEL for the repeated dose toxicity data is 200/3 or 66.66 mg/kg/day.

Therefore, the 1-(2,2,6-trimethylcyclohexyl)-3-hexanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1-(2,2,6-trimethylcyclohexyl)-3-hexanol NOAEL in mg/kg/day by the total systemic exposure to 1-(2,2,6-trimethylcyclohexyl)-3-hexanol, 66.66/0.0054, or 12344.

In addition, the total systemic exposure to 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (5.4 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.

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, 2020) and a reference dose of 0.67 mg/kg/day.

Derivation of reference dose (RfD)

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 reference dose for 1-(2,2,6-rimethylcyclohexyl)-3-hexanol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 66.66 mg/kg/day by the uncertainty factor, 100 = 0.67 mg/kg/day.

*The Expert Panel for Fragrances 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: 10/16/20.

11.1.3. Reproductive toxicity

The MOE for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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 1-(2,2,6-trimethylcyclohexyl)-3-hexanol. In an OECD TG 422 and GLP-compliant combined repeated dose toxicity study with a reproduction/development toxicity screening test, 12 SD Crl:CD rats/sex/dose were treated with 1-(2,2,6-trimethylcyclohexyl)-3-hexanol via gavage at doses of 0 (vehicle: corn oil), 60, 200, and 600 mg/kg/day. Males were treated once daily for 49 days (2 weeks prior to mating, during 2 weeks of mating, and 21 days of post-mating) before necropsy. Females were treated for 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. Additionally, 6 animals/sex/dose were included as recovery groups at 0 and 600 mg/kg/day for an additional 14 days. No treatment-related adverse effects were reported for mating, estrous cycle, or sperm parameters of animals at any of the dose levels. No abnormalities were reported in the integrity of the various cell types present within the different stages of the spermatogenic cycle, and no impairment in reproductive function was reported in either sex at any dose level. A significant reduction was reported in the total litter size of pups at 600 mg/kg/day, which was considered a treatment-related adverse effect. No treatment-related adverse effects were reported in mating period, mating index, gestation period, gestation index, post-implantation loss rate, live birth index, external examination of pups, body weights of pups, the sex ratio of pups, viability index, T4, TSH, anogenital distance, nipple retention, or endocrine-disruption potential at any dose level. Based on the absence of treatment-related adverse reproductive effects up to the highest dose tested, the NOAEL for fertility was considered as 600 mg/kg/day. Based on the reduction in the total litter size at 600 mg/kg/day, the NOAEL for developmental toxicity was considered as 200 mg/kg/day (RIFM, 2017e).

Therefore, the 1-(2,2,6-trimethylcyclohexyl)-3-hexanol MOE for the developmental toxicity endpoint can be calculated by dividing the 1-(2,2,6-trimethylcyclohexyl)-3-hexanol NOAEL in mg/kg/day by the total systemic exposure to 1-(2,2,6-trimethylcyclohexyl)-3-hexanol, 200/0.0054, or 37037.

The 1-(2,2,6-trimethylcyclohexyl)-3-hexanol MOE for the fertility endpoint can be calculated by dividing the 1-(2,2,6-trimethylcyclohexyl)-3-hexanol NOAEL in mg/kg/day by the total systemic exposure to 1-(2,2,6-trimethylcyclohexyl)-3-hexanol, 600/0.0054, or 111111.

In addition, the total systemic exposure to 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (5.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.4. Skin sensitization

Based on the available data, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is considered to be a skin sensitizer with a defined NESIL of 3100 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is considered a skin sensitizer with a NESIL of 3100 μg/cm^2. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; OECD Toolbox v4.2; Toxtree 3.1.0). No *in chemico* or *in vitro* predictive skin sensitization studies are available for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol. In a murine local lymph node assay (LLNA) BrdU-ELISA, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol was found to be sensitizing with an EC1.6 value of 12.73% (3182 μg/cm^2) (RIFM, 2017a). In guinea pigs, a Buehler test did not present reactions indicative of sensitization (RIFM, 1977). In a human maximization test conducted with 10% (6900 μg/cm^2) of 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (RIFM, 1985b), no skin sensitization reactions were observed in 22 subjects. Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2% of 1-(2,2,6-trimethylcyclohexyl)-3-hexanol in petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1984). In another CNIH, no reactions indicative of sensitization were observed in any of the 110 volunteers with 2.7% (3188 μg/cm^2) 1-(2,2,6-trimethylcyclohexyl)-3-hexanol in 1:3 EtOH:DEP (RIFM, 2017d).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is a weak skin sensitizer with a WoE NESIL of 3100 μg/cm^2 (see 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, 2020) and a reference dose of 0.67 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and existing data, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In human phototoxicity studies, no reactions indicative of phototoxic/photoallergenic responses were observed (RIFM, 1984). Based on existing human data and the lack of absorbance, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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: 11/03/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol is below the inhalation TTC Cramer Class I limit for local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 1-(2,2,6-trimethylcyclohexyl)-3-hexanol. Based on the Creme RIFM Model, the inhalation exposure is 0.027 mg/day. This exposure is 51.9 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.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/06/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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

Table 1
Data summary for 1-(2,2,6-trimethylcyclohexyl)-3-hexanol.

LLNA Weighted Mean EC1.6 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
3182.5 [1]	Weak	3188	6900	NA	3100

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.

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, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 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 1-(2,2,6-trimethylcyclohexyl)-3-hexanol as possibly persistent nor 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), 1-(2,2,6-trimethylcyclohexyl)-3-hexanol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key Studies

Biodegradation. **RIFM, 2009:** The inherent biodegradability of the test material was determined by the manometric respirometry test following the OECD 302C guidelines. Under the test conditions, the test material underwent 25% biodegradation after 28 days (50% biodegradation after 60 days).

RIFM, 1995: Biodegradability of the test material was determined in a BOD test for insoluble substances over 28 days of the test period. Under the conditions of the study, biodegradation of 12.43% was observed.

Ecotoxicity. **RIFM, 2005:** Short-term chronic toxicity tests with *Ceriodaphnia dubia* were conducted according to the EPA/600/4–90/027 and ASTM E729, 1997 methods under static conditions. The 7-day NOEC value for reproduction was reported to be 0.86 mg/L.

RIFM, 2005: Short-term chronic toxicity tests with immature fathead minnows, *Pimephales promelas*, were conducted according to the EPA/600/4–90/027 and ASTM E729, 1997 methods under static conditions. The 7-day NOEC values for growth and survival were reported to be 0.22 mg/L and 0.86 mg/L, respectively.

RIFM, 2017c: The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on mean measured concentrations was reported to be greater than 0.999 mg/L.

RIFM, 2017b: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value for growth rate and yield based on mean measured concentration was reported to be greater than 1 mg/L.

Other available data. 1-(2,2,6-Trimethylcyclohexyl)-3-hexanol has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

RIFM Framework Screening-level **(Tier 1)**	<u>0.150</u>			1,000,000	0.000150	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.070	<u>0.058</u>	0.185	10,000	0.0058	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.999		<u>0.22</u>	50	4.4	
Daphnia			0.86			
Algae						

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.8	5.8
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 4.4 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: 11/06/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&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 01/31/21.

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.

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