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RIFM fragrance ingredient safety assessment, 3,5,5-trimethyl-1-hexanol, CAS Registry Number 3452-97-9

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc, 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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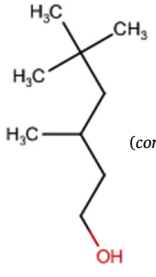

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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)
Creme RIFM Model – The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK – Derek Nexus is an *in silico* tool used to identify structural alerts
DRF – Dose Range Finding
DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
ECOSAR – Ecological Structure-Activity Relationships Predictive Model
EU – Europe/European Union
GLP – Good Laboratory Practice
IFRA – The International Fragrance Association
LOEL – Lowest Observed Effect Level
MOE – Margin of Exposure
MPPD – Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL – No Expected Sensitization Induction Level
NOAEC – No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
NOEC – No Observed Effect Concentration
NOEL – No Observed Effect Level
OECD – Organisation for Economic Co-operation and Development
OECD TG – Organisation for Economic Co-operation and Development Testing Guidelines
PBT – Persistent, Bioaccumulative, and Toxic
PEC/PNEC – Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery – In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA – Quantitative Risk Assessment
QSAR – Quantitative Structure-Activity Relationship
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD – Reference Dose
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
Statistically Significant – Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC – Threshold of Toxicological Concern
UV/Vis spectra – Ultraviolet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WoE – Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

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3,5,5-Trimethyl-1-hexanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,5,5-trimethyl-1-hexanol is not genotoxic. Data on 3,5,5-trimethyl-1-hexanol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across materials isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and isoamyl alcohol (CAS # 123-51-3) show that there are no safety concerns for 3,5,5-trimethyl-1-hexanol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3,5,5-trimethyl-1-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 3,5,5-trimethyl-1-hexanol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 3,5,5-trimethyl-1-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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1999; ECHA REACH Dossier 3,5,5-Trimethylhexan-1-ol; ECHA, 2012b)
Repeated Dose Toxicity: NOAEL = 4 mg/kg/day.	JECDB (1997)
Reproductive Toxicity: NOAEL = 12 mg/kg/day.	JECDB (1997)
Skin Sensitization: Not a sensitization concern.	(ECHA REACH Dossier: Isononyl alcohol; ECHA, 2011; Kern, 2010; RIFM, 1973)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 4% (OECD 301C)	(ECHA REACH Dossier: 3,5,5-Trimethylhexan-1-ol; ECHA, 2012b)
Bioaccumulation:	
Screening-level: 52.51 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 7.48 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: 7.48 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.748 μg/L	

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

1. Identification

1. **Chemical Name:** 3,5,5-Trimethyl-1-hexanol
2. **CAS Registry Number:** 3452-97-9
3. **Synonyms:** 1-Hexanol, 3,5,5-trimethyl-; 3,5,5-Trimethylhexanol; 3,5,5-Trimethylhexyl alcohol; i-Nonyl alcohol; Nonylol; 3,5,5-Trimethylhexan-1-ol; Trimethylhexanol; アルカノール(C = 5–38); Isononanol; 3,5,5-Trimethyl-1-hexanol
4. **Molecular Formula:** $C_9H_{20}O$
5. **Molecular Weight:** 144.25
6. **RIFM Number:** 1001
7. **Stereochemistry:** Isomer not specified. One chiral center present and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), 188.53 °C (EPI Suite)
2. **Flash Point:** 174 °F; CC (FMA), 76 °C (Globally Harmonized System)

3. **Log K_{ow}:** 3.0 (RIFM, 2009), 3.11 (EPI Suite)
4. **Melting Point**: −18.65 °C (EPI Suite)
5. **Water Solubility:** 572 mg/L (EPI Suite)
6. **Specific Gravity:** 0.832 (FMA)
7. **Vapor Pressure:** 0.0667 mm Hg at 20 °C (EPI Suite v4.0), 0.2 mm Hg at 20 °C (FMA), 0.106 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless oily liquid. Relatively powerful, oily-herbaceous, sweet odor in dilution. The overall impression is that of a "chemical" odor, rather than nondescript, hard, and, unless highly diluted, not very pleasant (Arctander, Volume II, 1969)

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.030% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000035 mg/kg/day or 0.0025 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00099 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)

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Isononyl alcohol (isomer unspecified) (CAS # 27458-94-2); isoamyl alcohol (CAS # 123-51-3)
   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 are available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

3,5,5-Trimethyl-1-hexanol is reported to occur in the following foods by the VCF*:

Black currants (*Ribes nigrum* L.)
Crab
Guava and Feyoa

*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 12/17/20 (ECHA, 2012b).

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, 3,5,5-trimethyl-1-hexanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3,5,5-trimethyl-1-hexanol was assessed in a GLP- and OECD 471-compliant Ames study. *Salmonella typhimurium strains* TA98, TA100, TA1535, TA1537, and TA102 were treated with 3,5,5-trimethyl-1-hexanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increases in the number of revertant colonies were observed (RIFM, 1999). Under the conditions of the study, 3,5,5-trimethyl-1-hexanol was considered not mutagenic in the Ames test.

The clastogenic activity of 3,5,5-trimethyl-1-hexanol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung fibroblast cells (V79) were treated with 3,5,5-trimethyl-1-hexanol at concentrations up to 0.2 μg/mL in the presence and absence of metabolic activation. No significant increases in the number of chromosomal aberrations were detected at the concentrations tested (ECHA, 2012b). Under the conditions of the study, 3,5,5-trimethyl-1-hexanol was considered not clastogenic in mammalian cells.

Based on the available data, 3,5,5-trimethyl-1-hexanol does not present a concern for genotoxic potential.

Additional References: Kusakabe (2002).

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

11.1.2. Repeated dose toxicity

The MOE for 3,5,5-trimethyl-1-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 3,5,5-trimethyl-1-hexanol for the repeated dose toxicity endpoint. An OECD 422 gavage, combined, repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in SD (CRJ:CD) rats. Groups of 12 rats/sex/dose were administered via gavage the test material, 3,5,5-trimethyl-1-hexanol, at doses of 0, 12, 60, or 300 mg/kg/day daily in an olive oil vehicle. Male rats were dosed for 46 days, while female rats were dosed 14 days before mating, throughout mating and gestation, until day 3 of lactation. At 300 mg/kg/day, one female died on gestation day 21, and 3 females were euthanized due to weakness from gestation days 14–19. Body weights and food consumption were decreased, and histopathological examination revealed liver and renal epithelial alterations in these animals. There was a statistically significant increase in the relative liver and kidney weights of mid- and high-dose group males and high-dose group females. Histopathological examination revealed a slight degree of irregularity in the shape of follicles, columnar change of the follicular epithelium, and a decrease of colloid in the thyroid in males of the 300 mg/kg/day group. In female rats, a slight degree of renal epithelial fatty change in the 60 and 300 mg/kg/day groups and atrophy of the thymus in the 300 mg/kg/day group were observed. Thus, the NOAEL for repeated dose toxicity was considered to be 12 mg/kg/day, based on increased liver and kidney weights in both sexes and renal epithelial fatty change in female rats (JECDB, 1997; ECHA, 2012b; OECD, 2002).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012a). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 12/3 or 4 mg/kg/day.

Therefore, the 3,5,5-trimethyl-1-hexanol MOE for repeated dose toxicity can be calculated by dividing the 3,5,5-trimethyl-1-hexanol NOAEL in mg/kg/day by the total systemic exposure to 3,5,5-trimethyl-1-hexanol, 4/0.00099, or 4040.

In addition, the total systemic exposure to 3,5,5-trimethyl-1-hexanol (0.99 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.

*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: RIFM, 2010a; RIFM, 2010b; Rhodes (1984).

Literature Search and Risk Assessment Completed On: 11/09/20.

11.1.3. Reproductive toxicity

The MOE for 3,5,5-trimethyl-1-hexanol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 3,5,5-trimethyl-1-hexanol for the developmental toxicity endpoint. An OECD 422 gavage combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in SD (CRJ:CD) rats. Groups of 12 rats/sex/dose were administered via gavage with test material, 3,5,5-trimethyl-1-hexanol at doses of 0, 12, 60, or 300 mg/kg/day daily in an olive oil vehicle. Male rats were dosed for 46 days, while female rats were dosed 14 days before mating, and throughout mating, gestation, and until day 3 of lactation. The implantation rate and the number of pups born alive decreased in the 60 and 300 mg/kg/day groups, which reached statistical significance. The viability index on day 4 of lactation was significantly decreased at 300 mg/kg/day, and male and female pups of the 300 mg/kg group showed statistically significantly reduced body weights on day 0 of lactation. Thus, the NOAEL for developmental toxicity was considered to be 12 mg/kg/day, based on reduced implantations and numbers of live pups (JECDB, 1997; ECHA, 2012b; OECD, 2002). There were no teratogenic effects observed, even at maternally toxic dose levels. **Therefore, the 3,5,5-trimethyl-1-hexanol MOE for developmental toxicity can be calculated by dividing the 3,5,5-trimethyl-1-hexanol NOAEL in mg/kg/day by the total systemic exposure to 3,5,5-trimethyl-1-hexanol, 12/0.00099, or 12121.**

There are sufficient data on 3,5,5-trimethyl-1-hexanol for the fertility endpoint. An OECD 422 gavage combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in SD (CRJ:CD) rats. Groups of 12 rats/sex/dose were administered via gavage with test material, 3,5,5-trimethyl-1-hexanol, at doses of 0, 12, 60, or 300 mg/kg/day daily in an olive oil vehicle. Male rats were dosed for 46 days, while female rats were dosed 14 days before mating, and throughout mating, gestation, and until day 3 of lactation. No fertility effects were observed in males, but prolonged diestrous was observed in females of the high-dose group. A statistically significant decrease in implantation index was observed in females of the 60 and 300 mg/kg/day dose groups. Thus, the NOAEL for reproductive toxicity in males was considered to be 300 mg/kg/day, the highest dosage tested. The NOAEL for reproductive toxicity in females was considered to be 12 mg/kg/day, based on decreased implantation index (JECDB, 1997; ECHA, 2012b; OECD, 2002). The most conservative NOAEL of 12 mg/kg/day was selected for the reproductive toxicity endpoint. **Therefore, the 3,5,5-trimethyl-1-hexanol MOE for fertility can be calculated by dividing the 3,5,5-trimethyl-1-hexanol NOAEL in mg/kg/day by the total systemic exposure to 3,5,5-trimethyl-1--hexanol, 12/0.00099, or 12121.**

In addition, the total systemic exposure to 3,5,5-trimethyl-1-hexanol (0.99 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2010a; RIFM, 2010b; Rhodes (1984).

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

11.1.4. Skin sensitization

Based on existing data and read-across to isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and isoamyl alcohol (CAS # 123-51-3), 3,5,5-trimethyl-1-hexanol does not present a concern for skin sensitization under the current, declared use level.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3,5,5-trimethyl-1-hexanol. Based on the existing data and read-across materials isoamyl alcohol (CAS # 123-51-3; see Section VI) and isononyl alcohol (isomer unspecified) (CAS # 27458-94-2; see Section VI), 3,5,5-trimethyl-1-hexanol does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1; OECD Toolbox v4.2). In a Buehler test, read-across material isononyl alcohol did not present reactions indicative of sensitization (ECHA, 2011). In a murine local lymph node assay (LLNA), read-across material isoamyl alcohol was found to be non-sensitizing up to 50% (12500 μg/cm^2) (Kern, 2010). In 2 separate human maximization tests, no reactions indicative of sensitization were observed with 8% 3,5,5-trimethyl-1-hexanol or 8% read-across material isoamyl alcohol (5520 μg/cm^2) (RIFM, 1977; RIFM, 1976). Based on the weight of evidence (WoE) from structural analysis, human data, and read-across materials isoamyl alcohol and isononyl alcohol (isomer unspecified), 3,5,5-trimethyl-1-hexanol does not present a concern for skin sensitization.

Additional References: RIFM, 2009; Abraham (1995); Patel (2002).

Literature Search and Risk Assessment Completed On: 12/09/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3,5,5-trimethyl-1-hexanol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 3,5,5-trimethyl-1-hexanol in experimental models. 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). Based on the lack of absorbance, 3,5,5-trimethyl-1-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: 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 3,5,5-trimethyl-1-hexanol 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 3,5,5-trimethyl-1-hexanol. Based on the Creme RIFM Model, the inhalation exposure is 0.0025 mg/day. This exposure is 560 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: 11/19/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3,5,5-trimethyl-1-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 Volume of Use, 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, 3,5,5-trimethyl-1-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 is > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 3,5,5-trimethyl-1-hexanol as possibly persistent but not 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, 2012a). 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).

11.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), 3,5,5-trimethyl-1--hexanol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 3,5,5-Trimethyl-1-hexanol has been registered under REACH and the following additional data are available (ECHA, 2012b):

The ready biodegradability of 3,5,5-trimethyl-1-hexanol was evaluated in the MITI-I test according to the OECD 301C method. Biodegradation was <4% BOD after 28 days of incubation.

An acute fish toxicity test using *Oryzias latipes* was conducted according to OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on time-weighted average concentration was reported to be 27.7 mg/L (95% CI: 16–37.1 mg/L).

A 14-day fish (*Oryzias latipes*) toxicity test according to OECD 204 guidelines was conducted under flow-through conditions. The 14-day LC50 value based on time-weighted average was greater than 20 mg/L, and the NOEC was reported to be 1.28 mg/L.

A *Daphnia magna* acute toxicity test was conducted according to the OECD 202 method. The EC50 (48 h) value based on time-weighted average concentration was reported to be 6.77 mg/L (95% CI: 5.88–7.71 mg/L).

A 21-day *Daphnia magna* reproduction test was conducted according to the OECD 202 part 2 method, under flow-through conditions. The 21-day NOEC was reported to be 1.46 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 value based on measured concentration for biomass, and growth inhibition was reported to be 19.5 mg/L and greater than 50 mg/L, respectively.

11.2.3. Risk assessment refinement

Since 3,5,5-trimethyl-1-hexanol 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 Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3	3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	26.24			1000000	0.02624	
ECOSAR Acute Endpoints (Tier 2) v1.11	11.889	7.48	8.519	10000	0.748	Neutral Organic

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

The RIFM PNEC is 0.748 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 Volume of Use.

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

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 09/31/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112861.

Appendix

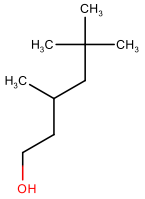
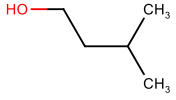
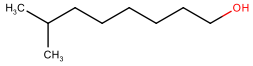
Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).

- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 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	Read-across Material
Principal Name	3,5,5-Trimethyl-1-hexanol	Isoamyl alcohol	Isononyl alcohol (isomer unspecified)
CAS No.	3452-97-9	123-51-3	27458-94-2
Structure			
Similarity (Tanimoto Score)		0.63	0.74
Endpoint		• Skin sensitization	• Skin sensitization
Molecular Formula	$C_9H_{20}O$	$C_5H_{12}O$	$C_9H_{20}O$
Molecular Weight	144.258	88.15	144.258
Melting Point (°C, EPI Suite)	−18.65	−117.20	64.50
Boiling Point (°C, EPI Suite)	194.00	131.10	206.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.41E+01	3.16E+02	2.64E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.12E+02	2.67E+04	4.61E+02
Log KOW	3.42	1.16	3.22
J_{max} (μg/cm^2/h, SAM)	41.50	733.51	52.79
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.17E+00	1.43E+00	4.17E+00
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found
Protein Binding (OECD)	No alert found	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)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	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	See Supplemental Data 3

Summary

There are insufficient toxicity data on 3,5,5-trimethyl-1-hexanol (CAS # 3452-97-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical−chemical properties, and expert judgment, isoamyl alcohol (CAS # 123-51-3) and isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Isoamyl alcohol (CAS # 123-51-3) was used as a read-across analog for the target material 3,5,5-trimethyl-1-hexanol (CAS # 3452-97-9) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of alcohols.
  - o The target material and the read-across analog share a common saturated aliphatic alcohol fragment.
  - o The key difference between the target material and the read-across analog is that the target has a C6 chain while the read-across material has a C4 chain.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by saturated aliphatic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical−chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.

- According to the OECD QSAR Toolbox, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- Data are consistent with *in silico* alerts.
- 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.

- Isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) was used as a read-across analog for the target material 3,5,5-trimethyl-1-hexanol (CAS # 3452-97-9) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to the class of alcohols.
  - The target material and the read-across analog share a common saturated aliphatic alcohol fragment.
  - The key difference between the target material and the read-across analog is that the target has a C6 chain while the read-across material has a C8 chain. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by saturated aliphatic alcohol fragment. 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, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Data are consistent with *in silico* alerts.
  - 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.

Explanation of Cramer Classification

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

Q1. Normal constituent of the body **No**
Q2. Contains functional groups associated with enhanced toxicity **No**
Q3. Contains elements other than C,H,O,N,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 hydrolyzed to a common terpene **No**
Q19. Open chain **Yes**
Q20. Aliphatic with some functional groups (see explanation) **Yes**
Q21. 3 or more different functional groups **No**
Q18. One of the list (see explanation) **No** Class Low (Class I)

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