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Short review

RIFM fragrance ingredient safety assessment, 3,7-dimethyl-1-octanol, CAS Registry Number 106-21-8

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1. Identification

1 **Chemical Name:** 3,7-dimethyl-1-octanol
2 **CAS Registry Number:** 106-21-8
3. **Synonyms:** dihydrocitronellol; 3,7-dimethyl-1-octanol; 1-Octanol, 3,7-dimethyl-; Tetrahydrogeraniol; Pelargol; 脂肪酸不飽和アルコール(C = 9 ~ 14); 3,7-dimethyloctan-1-ol
4 **Molecular Formula:** $C_{10}H_{22}O$
5 **Molecular Weight:** 158.29
6 **RIFM Number:** 360

2. Physical data

1 **Boiling Point:** 222 °C [FMA database], 216.17 °C [EPI Suite]
2 **Flash Point:** >190 °F; CC [FMA database]
3 **Log K_{OW}:** 3.9 at 35 °C [RIFM, 1999c], 3.64 [EPI Suite]
4 **Melting Point:** no melting temp btwn −100 °C & vaporization/decomp [RIFM, 2012a], −13.66 °C [EPI Suite]
5 **Water Solubility:** 64 mg/l ± 4 mg/l at T = 20 °C ± 0.5 °C [RIFM, 2012a], 175.4 mg/l [EPI Suite]
6 **Specific Gravity:** 0.834 [FMA database]

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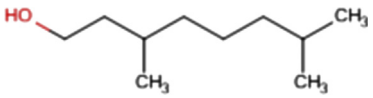
Name: 3,7-Dimethyl-1-octanol
CAS Registry Number: 106-21-8



Abbreviation list:
2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
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; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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
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
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultra Violet/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 under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Target data provided a MOE > 100 for the developmental toxicity endpoint. Data from the read across analog isoamyl alcohol (CAS # 123-51-3) show that this material is not genotoxic and provided a MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from the read across analogs isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and isoamyl alcohol (CAS # 123-51-3) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoints were evaluated and CAS # 106-21-8 was not found to be PBT; its risk quotients, based on current volume of use in Europe and North America, were acceptable (PEC/PNEC < 1).

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2001; RIFM, 2007)
Repeated Dose Toxicity: NOAEL = 1250 mg/kg/day.	(Schilling et al., 1997)
Developmental and Reproductive Toxicity: NOAEL = 450 and 300 mg/kg/day, respectively.	(RIFM, 2016a; ECHA REACH Dossier: 3-Methylbutan-1-ol)
Skin Sensitization: Not sensitizing.	(ECHA Dossier: Isononyl alcohol; Kern et al., 2010; RIFM, 1973)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 100% (OECD 302C)	(RIFM, 1999b)
Bioaccumulation: Screening Level: 117.2 l/kg	(EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 48-hr *Daphnia magna* LC50: 2.888 mg/l	(EpiSuite ver 4.1)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) >1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-hr *Daphnia magna* LC50: 2.888 mg/l	(EpiSuite ver 4.1)
RIFM PNEC is: 0.2888 μg/l	
• Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe <1	

7 **Vapor Pressure:** 0.0218 mm Hg @ 20 °C [EPI Suite 4.0], 0.06 mm Hg 20 °C [FMA database], 0.0356 mm Hg @ 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 liquid with sweet rose-like odor.

3. Exposure

1 **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2011)
2 **95th Percentile Concentration in Hydroalcoholics:** 0.031% (RIFM, 2016b)
3 **Inhalation Exposure*:** 0.00021 mg/kg/day or 0.015 mg/day (RIFM, 2016b)
4 **Total Systemic Exposure**:** 0.0026 mg/kg/day (RIFM, 2016b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 et al., 2015; Safford et al., 2015, 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2 **Analogues Selected:**
a. **Genotoxicity:** Isoamyl alcohol (CAS # 123-51-3)
b **Repeated Dose Toxicity:** Isoamyl alcohol (CAS # 123-51-3)
c **Developmental and Reproductive Toxicity:** Isoamyl alcohol (CAS # 123-51-3)
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

6. Metabolism

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

7. Natural occurrence (discrete chemical) or composition (NCS)

3,7-Dimethyl-1-octanol is reported to occur in the following foods*:

Citrus fruits
Honey
Rice (*Oryza sativa* L.)

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed on 05/23/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, 3,7-dimethyl-1-octanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 3,7-Dimethyl-1-octanol was tested in the BlueScreen assay and was found negative for genotoxicity in the presence and absence of metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013a). The mutagenic activity of 3,7-dimethyl-1-octanol (CAS # 106-21-8) 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 TA1535, TA1537, TA1538, TA98, TA100 and TA102 were treated with 3,7-dimethyl-1-octanol in DMSO (dimethyl sulfoxide) at concentrations up to 1500 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, 3,7-dimethyl-1-octanol was not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of 3,7-dimethyl-1-octanol. Read across can be made to isoamyl alcohol (CAS # 123-51-3; see Section 5) which was assessed for clastogenicity in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD 474. The test material was administered in corn oil via oral gavage, to groups of male and female NMRI mice (5/sex/dose). Doses of 500, 1000, and 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). Under the conditions of the study, isoamyl alcohol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the mutagenicity data available on the target material and the clastogenicity data on the read across analog, isoamyl alcohol does not present a concern for genotoxic potential; this can be extended to 3,7-dimethyl-1-octanol.

Additional References: Chen et al., 1984; Kreja and Seidel, 2001, 2002; Seidel and Plappert, 1999; Nakajima et al., 2006; RIFM, 2007.

Literature Search and Risk Assessment Completed on: 09/26/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for 3,7-dimethyl-1-octanol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3,7-dimethyl-1-octanol. Read across material, isoamyl alcohol (CAS # 123-51-3; see Section 5) has sufficient repeated dose toxicity data. A gavage OECD 422 combined repeated dose toxicity study was conducted on groups of 12 male and female Sprague-Dawley rats/group and they were administered the test material, isoamyl alcohol via gavage at doses of 0, 30, 100 and 300 mg/kg/day, and an additional satellite recovery group of 5 animals/sex/group were administered the test material at doses of 0 and 300 mg/kg/day. The males were administered test material for 42 days (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and for 42 days in the satellite recovery group. The vehicle used to administer the test material was 1 w/v% CMC solution containing 1% Tween 80 in water. There was a reduction in body weight gains among high dose males. The body weight gains among high dose recovery group animals was comparable to controls. Thus, the NOAEL was determined to be 100 mg/kg/day, based on reduced body weight gain in the males (ECHA REACH Dossier: 3-Methylbutan-1-ol, accessed 07/09/14). In another study, an OECD/GLP 408, 13-week study was conducted on groups of 10 SPF-Wistar, Chbb:THOM rats/sex/group and they were administered the test material, isoamyl alcohol via drinking water at concentrations of 0, 1000 ppm (about 80 mg/kg/day), 4000 ppm (about 340 mg/kg/day) and 16,000 ppm (about 1250 mg/kg/day). Although there were slight alterations in the hematological parameters, the NOAEL was determined to be 16000 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment-related (Schilling et al., 1997, data also available in RIFM, 1991). In another study, groups of 15 rats/sex/group were gavaged with the test material, isoamyl alcohol at doses of 0, 150, 500 and 1000 mg/kg/day for 17 weeks. There were no adverse effects reported due to the test material administration up to the highest dose tested. Thus, the NOAEL was determined to be 1000 mg/kg/day (Carpanini et al., 1973). Since the NOAEL from the OECD 422 study was based on reduction in body weight gains among males only and the body weight gains among animals of the high dose recovery group animals were similar to that of the control, this was not considered towards deriving a NOAEL for 3,7 dimethyl-1-octanol. Since no adverse effects were reported among the animals during the longer duration 13- and 17-week studies, the NOAEL was determined to be 1250 mg/kg/day, the highest dose tested. **Therefore, the 3,7-dimethyl-1-octanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyl-1-octanol, 1250/0.0026 or 480769.**

In addition, the total systemic exposure to 3,7-dimethyl-1-octanol (2.6 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: ECHA REACH Dossier: 3-Methylbutan-1-ol; RIFM, 1992.

Literature Search and Risk Assessment Completed on: 10/21/2016.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3,7-dimethyl-1-octanol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. The developmental toxicity data on 3,7-dimethyl-1-octanol are sufficient for the developmental toxicity endpoint. An OECD 414 GLP gavage prenatal developmental toxicity study was conducted with test material, 3,7-dimethyl-1-octanol on groups of 25 time-mated female Wistar rats/groups. The animals were administered the test material via gavage at doses of 0 (corn oil), 50, 150 and 450 mg/kg/day on gestation days (GD) 6–19. The animals were euthanized on GD 20. There were no other alterations reported among the treated dams and the developing fetus as compared to the control up to the highest dose tested. The NOAEL for the developmental toxicity endpoint was determined to be 450 mg/kg/day, the highest dose tested (RIFM, 2016a). **Therefore, the 3,7-dimethyl-1-octanol MOE for the developmental toxicity endpoint can be calculated by dividing the 3,7-dimethyl-1-octanol NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyl-1-octanol, 450/0.0026 or 173077.**

There are limited reproductive toxicity data on 3,7-dimethyl-1-octanol. A 14-day screening study for reproductive toxicity in male rats was done on 3,7-dimethyl-1-octanol. There were no adverse effects on male reproductive organs or sperm parameters at 1000 mg/kg/day, the only dose tested (RIFM, 2013b). Since there are no female reproductive toxicity data on 3,7-dimethyl-1-octanol, a NOAEL could not be identified for the reproductive toxicity endpoint. Read across material, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient reproductive toxicity data. An OECD 422 gavage (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) was conducted on groups of 12 Sprague-Dawley rats/sex/group which were administered test material, isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. . The vehicle used to administer the test material was 1 w/v% CMC solution containing 1% Tween 80 in water. The males were administered test material for 42 days (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and for 42 days in the satellite recovery group. There were no signs of toxicity towards the reproductive performance of the parental generation animals up to the highest dose tested (ECHA REACH Dossier: 3-Methylbutan-1-ol). Since there are no female reproductive toxicity data on 3,7-dimethyl-1-octanol, the most conservative NOAEL of 300 mg/kg/day from the OECD 422 study on isoamyl alcohol was selected for the reproductive toxicity endpoint. **Therefore, the 3,7-dimethyl-1-octanol MOE for the reproductive toxicity endpoint can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyl-1-octanol, 300/0.0026 or 115385.**

In addition, the total systemic exposure to 3,7-dimethyl-1-octanol (2.6 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: ECHA REACH Dossier: 3-Methylbutan-1-ol; RIFM, 1992.

Literature Search and Risk Assessment Completed on: 10/21/2016.

10.1.4. Skin sensitization

Based on existing data and read across to isononyl alcohol (isomer unspecified) (CAS # 27458-94-2); isoamyl alcohol (CAS # 123-51-3), 3,7-dimethyl-1-octanol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3,7-dimethyl-1-octanol. Based on the existing data and read across materials isoamyl alcohol (CAS # 123-51-3; see Section 5) and isononyl alcohol (isomer unspecified) (CAS # 27458-94-2; see Section 5), 3,7-dimethyl-1-octanol 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 et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a guinea pig open epicutaneous test 8% 3,7-dimethyl-1-octanol was reported as non-sensitizing (Klecak, 1979). In a Buehler test, read across material isononyl alcohol did not present reactions indicative of sensitization (ECHA REACH Dossier: Isononyl alcohol, accessed 9/30/2016). 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 et al., 2010). In two separate human maximization tests, no reactions indicative of sensitization were observed with 8% 3,7-dimethyl-1-octanol or 8% read across material isoamyl alcohol (5520 μg/cm^2) (RIFM, 1973; RIFM, 1976). Based on weight of evidence from structural analysis, human data and read across materials isoamyl alcohol and isononyl alcohol (isomer unspecified), 3,7-dimethyl-1-octanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/28/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 3,7-dimethyl-1-octanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3,7-dimethyl-1-octanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L · mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 3,7-dimethyl-1-octanol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3,7-dimethyl-1-octanol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3,7-dimethyl-1-octanol. Based on the Creme RIFM model, the inhalation exposure is 0.015 mg/day. This exposure is 93 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3,7-dimethyl-1-octanol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 3,7-dimethyl-1-octanol 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 EPISUITE ver 4.1 did not identify 3,7-dimethyl-1-octanol as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3,7-dimethyl-1-octanol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 1999a**: The ready biodegradability of the test material was determined by the manometric respirometry according to the OECD 301 F method. Under the conditions of the study, biodegradation of 60% was observed.

RIFM, 1999b: The inherent biodegradability of the test material was determined by the respirometric method following the OECD 302C method. Biodegradation of 100% was observed after 32 days.

RIFM, 2000b: A study was performed to assess the biodegradability of the test material using the closed bottle test according to the OECD 301D method. Under the conditions of the study, biodegradation of 57% was observed.

RIFM, 2012b: The ready biodegradability of the test material was evaluated according to the OECD 301 B method. Biodegradation of 79% was observed after 28 days.

RIFM, 2012c: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301 F. The test material underwent 76% biodegradation in 28 days under the test conditions.

10.2.3.2. Ecotoxicity. **RIFM, 2000a**: The acute immobilization of the test material to *Daphnia magna* was evaluated according to the 92/69/EEC Part C, Method 2 under static conditions over a duration of 48 h. The geometric mean of EC 0/EC 100 at 48 h was 3.6 mg/l.

10.2.3.3. Other available data. 3,7-Dimethyl-1-octanol has been registered under REACH, but no additional data is available.

10.2.4. Risk assessment refinement

Since 37-dimethyl-1-ocanol has passed the screening criteriameasured data are included in this document for completeness only and have 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	4.75 mg/l			1,000,000	0.00474 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.371 mg/l	2.89 mg/l	4.025 mg/l	10,000	0.2888 μg/l	Neutral Organic SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.9	3.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–100	10–100
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 0.2888 μg/l. The revised PEC/PNECs for EU and NA <1 and, therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 06/16/14.

11. Literature search*

- **RIFM database**: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA**: http://echa.europa.eu/
- **NTP**: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder**: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED**: http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET**: http://toxnet.nlm.nih.gov/
- **IARC**: (http://monographs.iarc.fr):
- **OECD SIDS**: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor**: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS**: http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary**: http://cfpub.epa.gov/hpv-s/
- **Japanese NITE**: http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base**: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google**: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.07.039.

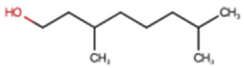
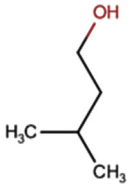
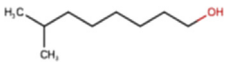
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.07.039.

Appendix. Read across justification

Methods

- The identified read-across analogues were confirmed by using expert judgment.
- The physicochemical properties of target and analogues were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogues were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material	
Principal Name	3,7-Dimethyl-1-octanol	Isoamyl alcohol	Isononyl alcohol (isomer unspecified)
CAS No.	106-21-8	123-51-3	27458-94-2
Structure			
Similarity (Tanimoto score)		0.58	0.62
Read across endpoint		• Genotoxicity • Repeated dose • Developmental and reproductive • Skin sensitization	• Skin sensitization
Molecular Formula	$C_{10}H_{22}O$	$C_5H_{12}O$	$C_9H_{20}O$
Molecular Weight	158.29	88.15	144.58
Melting Point (°C, EPISUITE)	−13.66	−61.49	−14.04
Boiling Point (°C, EPISUITE)	216.17	123.17	208.49
Vapor Pressure (Pa @ 25 °C, EPISUITE)	4.74	512	2.63
Log Kow (KOWWIN v1.68 in EPISUITE)	3.9[1]	1.16[2]	3.22
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	175.4	26700	461
J_{max} (mg/cm^2/h, SAM)	65.909	733.512	50.676
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	5.47E-005	1.33E-005	4.12E-005
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder, non-cyclic structure	• Non binder, non-cyclic structure	
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• toxicant (good reliability)	
Skin Sensitization			
Protein binding by OASIS v1.1	• No alert found	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (moderate reliability)	• Non-sensitizer (good reliability)	• Non-sensitizer (moderate reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

1. RIFM, 1999c
2. Patel et al., 2002

Summary

There are insufficient toxicity data on 3,7-dimethyl-1-octanol (CAS # 106-21-8). Hence, *in-silico* evaluation was conducted by determining read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, analogs isoamyl alcohol (CAS # 123-51-3) and isononyl alcohol (CAS # 27458-94-2) were identified as proper read across materials with data for their respective toxicity endpoints.

Conclusion/Rationale

- For the target material 3,7-dimethyl-1-octanol (CAS # 106-21-8), the following materials could be used as structurally similar read across analogs for the respective endpoints. Isoamyl alcohol (CAS # 123-51-3) for the skin senzitization, genotoxicity, repeated dose toxicity, reproductive and developmental toxicity endpoints and isononyl alcohol (CAS # 27458-94-2) for the skin senzitization endpoint.
  - The target substance and the read across analogs are structurally similar and belong to a class of saturated branched chain alkyl primary alcohols.
  - The target substance and read across analogs has 1-methyl pentanol fragment common among them.

- The key difference between the target substance and the read across analogs is that the target substance has a longer aliphatic chain by 4 carbons compared to the read across analog isoamyl alcohol, and the target substance has shorter aliphatic chain by 1 carbon compared to the read across analog isononyl alcohol.
- The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 1-methyl pentanol fragment. The differences in the structure which are responsible for the Tanimoto score < 1 are not relevant from a toxicity endpoint perspective.
- The target substance and the read across analogs have similar physical chemical properties. The J_{max} value of the target and the read across analogs appear to be different but with the calculated J_{max}, the read across analog substances and the target are predicted to have skin absorption up to 80%. Other differences in some of the physical chemical properties of the target substance and the read across analogs are estimated to be toxicologically insignificant for the genotoxicity, skin sensitization, developmental and reproductive toxicity, or repeated dose toxicity endpoints.
- According to the QSAR OECD Toolbox (V3.4), structural alerts for the respective toxicological endpoints are consistent between the target substance and the read across analogs.
- The CAESAR model for skin sensitization predicts the target substance to be a sensitizer while the read across analogs isoamyl alcohol and isononyl alcohol (isomer unspecified) are predicted to be non-sensitizers. All other skin sensitization protein binding alerts for the target substance and the read across analogs are negative. The data described in skin sensitization section show that the read across analogs pose no concern for the skin sensitization endpoint. Based on comparison of structure similarity, physical-chemical properties and reactivity predictions between the read across analogs and the target substance, the alert for the target will be superseded by the availability of data for the read across analog. In addition, according to the CAESAR model, the read across analogs is predicted to be a toxicant with good reliability for the developmental endpoint. The data described above in the developmental toxicity section show that the margin of exposure for the read across substance is adequate at the current level of use. So, in this case, the *in silico* prediction will be superseded.
- The target substance and the read across analogs are expected to be metabolized similarly as shown by metabolism simulator in the table above.
- The structural alerts for the respective toxicological endpoints are consistent between the metabolites of the read across analogs and the target substance.
- The structural differences between the target substance and the read across analogs are deemed to be toxicologically insignificant for the respective toxicological endpoints.

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