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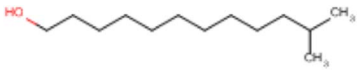
Short review

RIFM fragrance ingredient safety assessment, Alcohols, C11-14-iso-, C13-rich, CAS Registry Number 68526-86-3

A.M. Api[a,*], D. Belsito[b], D. Botelho[a], D. Browne[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], R. Parakhia[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a], J. Wahler[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany*
[f] *Member RIFM 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 RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA*
[i] *Member RIFM 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 RIFM 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 RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA*
[l] *Member RIFM 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 RIFM 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*

Version: 042617. This version replaces any previous versions.
Name: Alcohols, C11-14-iso-, C13-rich
CAS Registry Number: 68526-86-3
Additional CAS Numbers: 27458-92-0
Isotridecan-1-ol*
*The materials included in this assessment are a commercial mixture of alcohols



* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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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 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 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, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the read-across analog isodecyl alcohol (CAS # 25339-17-7) show that this material is not genotoxic. 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 reproductive toxicity and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The repeated dose toxicity endpoint was completed using data on the target material, which provided a MOE > 100. The developmental toxicity endpoint was completed using data from the target material and from the read-across analog alcohols, C7-9-iso-, C8-rich (CAS # 68526-83-0) which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on the target material; the material is not phototoxic/photoallergenic. The environmental endpoints were evaluated and the material was not found to be a 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, 1989a; ECHA REACH Dossier: alcohols, C9-11-iso-, C10-rich)
Repeated Dose Toxicity: 100 mg/kg/day.	(EPA Revised Robust Summaries: Olefin Hydroformylation Products Category)
Developmental and Reproductive Toxicity: Developmental NOAEL = 500 mg/kg/day. No Reproductive NOAEL available. Exposure < TTC (acceptable).	(EPA Revised Robust Summaries: Olefin Hydroformylation Products Category)
Skin Sensitization: Not sensitizing.	(ECHA REACH Dossier: isononyl alcohol (unspecified isomer); Kern et al., 2010)
Phototoxicity/ Photoallergenicity: Not phototoxic/ photoallergenic.	(UV Spectra, RIFM DB; RIFM, 1990)

Local Respiratory Toxicity: No NOAEC available. Exposure < TTC (acceptable).

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 61% (OECD 301F)	(ECHA REACH Dossier: alcohols, C11-14-iso-, C13-rich)
Bioaccumulation: Critical Measured Value: BCF: < 100 (OECD 305)	(ECHA REACH Dossier: alcohols, C11-14-iso-, C13-rich)
Ecotoxicity: Screening Level: 48-hr *Daphnia magna* LC50: 0.172 mg/l	(Epi Suite ver 4.1)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)

Critical Ecotoxicity (Epi Suite ver 4.1)

Endpoint: 48-hr *Daphnia magna* LC50: 0.172 mg/l

RIFM PNEC is: 0.0172 µg/l

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe < 1

1. Identification

Chemical Name: alcohols, C11-14-iso-, C13-rich	Chemical Name: isotridecan-1-ol
CAS Registry Number: 68526-86-3	**CAS Registry Number:** 27458-92-0
Synonyms: Alcohol C-13 (alcohols, C11-14-iso, C 13-rich); Alcohols, C11-14-iso-, C13-rich; Alcool oxo C 13 (isotridecyl alcohol)	**Synonyms:** isotridecan-1-ol; 11-methyldodecan-1-ol; アルカノール (C = 5 ~ 38)
Molecular Formula: Not Available	**Molecular Formula:** $C_{13}H_{28}O$
Molecular Weight: 200.37	**Molecular Weight:** 200.66
RIFM Number: 7027	**RIFM Number:** 5633

2. Physical data**

1. **Boiling Point**: 279.35 °C [EPI Suite v. 4.0]
2. **Flash Point**: > 200.00 °F TCC (> 93.33 °C)*
3. **Log K_{OW}**: 5.19 [EPI Suite v. 4.0]
4. **Melting Point**: 29.19 °C [EPI Suite v. 4.0]
5. **Water Solubility**: 5.237 mg/l [EPI Suite v. 4.0]
6. **Specific Gravity**: 0.84200 to 0.84700 @ 25.00 °C*
7. **Vapor Pressure**: 0.000462 mm Hg @ 25 °C [EPI Suite v. 4.0], 0.000233 mmHg @ 20 °C [EPI Suite 4.0]
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**: A colorless to pale yellow, clear liquid.*

*http://www.thegoodscentscompany.com/data/rw1317391.html, retrieved 4/9/2015.

**Physical data is identical for both materials included in this assessment.

3. Exposure***

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA , 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.14% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.00028 mg/kg/day or 0.020 mg/day (RIFM, 2015)
4. **Total Systemic Exposure **:** 0.0045 mg/kg/day (RIFM, 2015)

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials is recorded here for the 95th percentile concentration in hydroalcoholics, inhalation exposure and total exposure.

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 Toxicity

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

2. Analogues Selected:
   a. **Genotoxicity:** isodecyl alcohol (CAS # 25339-17-7)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** alcohols, C7-9-iso-, C8-rich (CAS # 68526-83-0)
   d. **Skin Sensitization:** isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and 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.

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

Alcohols, C11-14-iso-, C13-rich are not reported to occur in food by the VCF* and are not found in natural complex substances (NCS).

Isotridecan-1-ol is reported to occur in the following foods* and is not found in natural complex substances (NCS):

Beef

*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

Alcohols, C11-14-iso-, C13-rich and isotridecan-1-ol have dossiers available, accessed 4/9/2015.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, alcohols, C11-14-iso-, C13-rich do not present a concern for genotoxicity.

10.1.2. Risk assessment

Alcohols, C11-14-iso-, C13-rich were assessed in the BlueScreen assay and found negative for genotoxicity with and without metabolic activation, indicating a lack of concern for genotoxicity (RIFM, 2013). There are no studies assessing the mutagenic activity of alcohols, C11-14-iso-, C13-rich. The additional material included in this assessment, isotridecanol (CAS # 27458-92-0), was assessed in a GLP compliant Ames assay conducted in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were treated with isotridecan-1-ol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increase in the frequency of revertant colonies was observed (RIFM, 1989a). Under the conditions of the study, isotridecan-1-ol was considered not mutagenic in bacterial gene mutation study and this can be extended to alcohols, C11-14-iso-, C13-rich.

There are no studies assessing the clastogenic activity of alcohols, C11-14-iso, C13-rich or isotridecanol. The clastogenicity of read-across material isodecyl alcohol (CAS # 25339-17-7; see section 5) was assessed in a chromosome aberration assay conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells (CHO) were treated with isodecyl alcohol in DMSO at the concentrations up to 160 μg/ml with and without metabolic activation. No significant increases in structural chromosomal aberrations were observed in any of the test conditions (ECHA REACH Dossier: alcohols, C9-11-iso-, C10-rich). Under the conditions of the study, isodecyl alcohol was considered not clastogenic in the chromosome aberration assay and this can be extended to alcohols, C11-14-iso-, C13-rich.

Based on the available data, alcohols, C11-14-iso-, C13-rich do not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/28/2016.

10.1.3. Repeated dose toxicity

The margin of exposure for alcohols, C11-14-iso-, C13-rich is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. Alcohols, C11-14-iso-, C13-rich, were combined with isotridecan-1-ol (CAS # 27458-92-0; see section 1). There are sufficient repeated dose toxicity data on alcohols, C11-14-iso-, C13-rich. In an OECD 408 study, test material alcohols, C11-C14-iso-, C13- rich was administered via gavage for 90 days to Sprague-Dawley rats at doses of 0, 100, 500 or 1000 mg/kg/day. The NOAEL was determined to be 100 mg/kg/day, based on decreased body weight, hematological changes and increased organ weights at higher dose levels. The histopathological examination showed no adverse effects (EPA Revised Robust Summaries: Olefin Hydroformylation Products Category). Therefore, the alcohols, C11-14-iso-, C13-rich MOE for the repeated dose toxicity endpoint can be calculated by dividing the alcohols, C11-14-iso-, C13-rich NOAEL in mg/kg/day by the total systemic exposure to alcohols, C11-14-iso-, C13-rich, 100/0.0045 or 22222.

In addition, the total systemic exposure to alcohols, C11-14-iso-, C13-rich (4.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2010.

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

10.1.4. Developmental and reproductive toxicity

The margin of exposure for alcohols, C11-14-iso-, C13-rich is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on alcohols, C11-14-iso-, C13-rich or any read-across materials. The total systemic exposure to alcohols, C11-14-iso-, C13-rich is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.5. Risk assessment

Alcohols, C11-14-iso-, C13-rich, was combined with isotridecan-1-ol (CAS # 27458-92-0; see section 1). There are no developmental toxicity data on alcohols, C11-14-iso-, C13-rich, however, there are sufficient developmental toxicity data on isotridecan-1-ol. In an OECD 414 gavage study, pregnant rats received test material isotridecan-1-ol at doses of 0 (olive oil), 60, 250 or 750 mg/kg/day on days 6–19 of gestation. Maternal toxicity at 750 mg/kg/day included clinical signs, decreased food consumption and increased liver weight and associated alterations in clinical chemistry parameters. There were no adverse effects on the fetuses. The NOAEL for maternal toxicity was determined to be 250 mg/kg/day and the NOAEL for developmental toxicity was 750 mg/kg/day, the highest dose tested (RIFM, 2003c). Additionally, an OECD 414 study was conducted on read-across material alcohols, C7-9-iso-, C8-rich (CAS # 68526-83-0; see section 5) on four groups of Crl:CDBR female rats at doses of 0 (corn oil), 100, 500 or 1000 mg/kg/day. The test material was administered via gavage to the pregnant rats on days 6–15 of gestation. Maternal toxicity in the high dose group included clinical signs, decreased body weight and food consumption and post-implantation loss. There were skeletal variations in the fetuses of the mid- and high-dose groups, however, the effects were not considered adverse. Thus, the NOAEL for maternal and developmental toxicity was 500 mg/kg/day (EPA Revised Robust Summaries: Olefin Hydroformylation Products Category). The most conservative NOAEL of 500 mg/kg/day for alcohols, C7-9-iso-, C8-rich (CAS # 68526-83-0) was considered. Therefore, the alcohols, C11-14-iso-, C13-rich MOE for the developmental toxicity endpoint can be calculated by dividing the alcohols, C7-9-iso-, C8-rich NOAEL in mg/kg/day by the total systemic exposure to alcohols, C11-14-iso, C13-rich, 500/0.0045 or 111111.

In addition, the total systemic exposure to alcohols, C11-14-iso-, C13-rich (4.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are limited reproductive toxicity data on alcohols, C11-14-iso-, C13-rich, isotridecan-1-ol or any read-across materials that can be used to support the reproductive toxicity endpoint. In an OECD 408 90-day gavage study in rats, alcohols, C11-14-iso-, C13-rich was administered at doses of 100, 500 or 1000 mg/kg/day. The males in the middle and high dose groups had significantly lower body weights and food consumption than the control animals. However, the females did not display any differences in body weight or food consumption. The males of the high dose group had higher relative testes weights compared to the controls. There were no histopathological findings in the testes and the changes were considered most likely a consequence of the body weight effects. There were also no histopathological changes observed in the female reproductive organs (see repeated dose toxicity study above; EPA Revised Robust Summaries: Olefin Hydroformylation Products Category). The standard OECD 408 protocol does not require sufficient analysis of sperm and estrus cycles to evaluate the reproductive toxicity endpoint. The total systemic exposure to alcohols, C11-14-iso-, C13-rich (4.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

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

10.1.6. Skin sensitization

Based on the existing data for read-across materials isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and isoamyl alcohol (CAS # 123-51-3), alcohols, C11-14-iso-, C13-rich do not present a concern for skin sensitization.

10.1.7. Risk assessment

No skin sensitization studies are available for alcohols, C11-14-iso-, C13-rich. 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), alcohols, C11-14-iso-, C13-rich 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 (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a Buehler test, read-across material isononyl alcohol (isomer unspecified) did not present reactions indicative of sensitization (ECHA REACH Dossier: isononyl alcohol (isomer unspecified). 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 a human maximization test, there were no reactions indicative of sensitization with 8% of the read-across material isoamyl alcohol (5520 μg/cm^2) (RIFM, 1975). Based on weight of evidence from structural analysis and read-across materials isoamyl alcohol and isononyl alcohol (isomer unspecified), alcohols, C11-14-iso-, C13-rich does not present a concern for skin sensitization.

Additional References: None.

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

10.1.8. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available *in vivo* experimental data, alcohols, C11-14-iso-, C13-rich would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.9. Risk assessment

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). In a phototoxicity study conducted with Himalayan spotted guinea pigs, topical application of 1, 3, 10 and 30% alcohols, C11-14-iso-, C13-rich in ethanol did not result in phototoxic reactions (RIFM, 1990). Based on lack of absorption and available *in vivo* experimental data, alcohols, C11-14-iso-, C13-rich would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.10. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, alcohols, C11-14-iso-, C13-rich, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.11. Risk assessment

There are limited inhalation data available on alcohols, C11-14-iso-, C13-rich. Based on the Creme RIFM model, the inhalation exposure is 0.020 mg/day. This exposure is 70 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: RIFM, 1963a; RIFM, 1963b.

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 alcohols, C11-14-iso-, C13-rich 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, alcohols, C11-14-iso-, C13-rich 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 ver 4.1 did not identify alcohols, C11-14-iso-, C13-rich as 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 EPI SUITE 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), alcohols, C11-14-iso-, C13-rich presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Biodegradation

For CAS # 27458-92-0:

RIFM, 1988: The Manometric Respirometry Test according to the EEC Directive 79–831 C.4. D method was conducted to determine the biodegradability of the test material. The test material underwent 98% biodegradation after 28 days.

RIFM, 1999: The ready biodegradability of the test material was evaluated according to the ISO 9439 method. Biodegradation of 90–100% was observed after 28 days.

10.2.3.1. Ecotoxicity. RIFM, 2003a: An algae inhibition study was conducted according to the OECD 201 method. The 72-h EbC50 was determined to be 1.30 mg/l, and the ErC50 was 1.63 mg/l.

RIFM, 2003b: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 0.391 mg/l.

RIFM, 1989b: A 96-h fish (Golden Orfe) acute toxicity study was evaluated according to the DIN 38412 method. The LC50 was determined to be between 4.64 and 10.0 mg/l.

RIFM, 2003d: A 96-h fish (Zebra fish) acute toxicity study was conducted according to the OECD method under semi-static conditions. Based upon the results of this study, the 96-h LC50 value for the test article was 0.55 mg/l (analytically determined concentration).

10.2.3.2. Other available data. Alcohols, C11-14-iso-, C13-rich (both

CAS numbers) have been registered under REACH and the additional data are available.

For CAS # 68526-86-3:

Ready biodegradability of the test material was evaluated according to the OECD 301F method. After 28 days, biodegradation of 61% was observed.

A fish bioaccumulation study was conducted with Rainbow trout according to the OECD 305 method. The BCF was reported to be 54.3.

A fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 was reported to be 0.42 mg/l.

An algae inhibition test was conducted according to the OECD 201 guidelines. The 72-h EC50 was reported to be 2.6 mg/l and 3.2 mg/l for biomass and growth rate, respectively.

For CAS # 27458-92-0:

An algae inhibition study was conducted according to the OECD 201 method. The 72-h ErC50 was reported to be 0.297 mg/l.

Daphnia magna reproduction study was conducted according to the OECD 211 method under semi-static conditions. The EC10 was 0.033 mg/l and 0.013 mg/l for mortality and reproductions, respectively. The 21-day NOEC was reported to be 0.014 mg/l for both mortality and reproductions.

A fish bioaccumulation study was conducted with Rainbow trout according to the OECD 305 method. The BCF was reported to be < 100.

10.2.3.3. Risk assessment refinement. Since alcohols, C11-14-iso-, C13-rich have passed the screening criteria, measured data is included in this document 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.4533 mg/l			1,000,000	0.0004533 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	0.226 mg/l	0.172 mg/l	0.433 mg/l	10,000	0.0172 µg/l	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.19	5.19
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10-100*	1-10*
Risk Characterization: PEC/PNEC	< 1	< 1

*Combined volumes for both CAS#.

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

The RIFM PNEC is 0.0172 µg/l. The revised PEC/PNECs for EU and NA are < 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: 5/13/15.

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.2017.10.048.

Transparency document

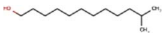
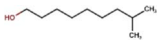
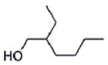
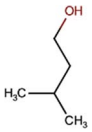
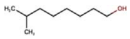
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.048.

Appendix

Read-across justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax 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 analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The shaded boxes below represent the endpoints that were not run in the models because those endpoints did not use those materials as read across; it is not necessary to compare the physical-chemical properties or alerts.

	Target material	Read-across material			
Principal Name	Alcohols, C11-14-iso-, C13-rich	Isodecyl alcohol	Alcohols, C7-9-iso-, C8-rich	Isoamyl alcohol	Isononyl alcohol (isomer unspecified)
CAS No.	**68526-86-3** and 27458-92-0	25339-17-7	68526-83-0	123-51-3	27458-94-2
Structure					
Similarity (Tanimoto score)		0.89	NA[a]	0.15	0.48
Read-across endpoint		• Genotoxicity	• Developmental and reproductive	• Skin sensitization	• Skin sensitization
Molecular Formula	$C_{13}H_{28}O$	$C_{10}H_{22}O$	$C_8H_{18}O$	$C_5H_{12}O$	$C_9H_{20}O$
Molecular Weight	200.37	158.85	130.23	88.15	144.58
Melting Point (°C, EPI SUITE)	29.19	−2.83	−25.50	−61.49	−14.04
Boiling Point (°C, EPI SUITE)	279.35	227.56	188.52	123.17	208.49
Vapor Pressure (Pa @ 25 °C, EPI SUITE)	0.0615	512	20.1	512	2.63
Log Kow (KOWWIN v1.68 in EPI SUITE)	5.19	3.71	2.73	1.16[1]	3.22
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	5.237	151.8	647	26 700	461
J_{max} (mg/cm^2/h, SAM)	3.828	46.220	58.78	733.512	50.676
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.28E-004	5.47E-005	3.10E-005	1.33E-005	4.12E-005
Genotoxicity					
DNA binding (OASIS v1.4 QSAR Toolbox v3.4)	• No alert found	• No alert found			
DNA binding by OECD QSAR Toolbox (v3.4)	• 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 v1.1	• 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			

Developmental and Reproductive toxicity					
ER Binding by OECD QSAR Tool Box (v3.4)	• Non binder, non-cyclic structure		• Non binder, non-cyclic structure		
Developmental Toxicity Model by CAESAR v2.1.6	• Non toxicant (low reliability)		• Non toxicant (low 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) (v2.1.6)	• Sensitizer (good reliability			• Non sensitizer (good reliability)	• Non sensitizer (moderate reliability)
Metabolism					
OECD QSAR Toolbox (v3.4) Rat liver S9 metabolism simulator	See supplemental data 1	See supplemental data 2	See supplemental data 3	See supplemental data 4	See supplemental data 5

NAa: This material is either a mixture or has multiple structures.
1. Patel et al., 2002.

Summary

There are insufficient toxicity data on alcohols, C11-14-iso-, C13-rich (CAS # 68526-86-3). 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, suitable analogs isodecyl alcohol (CAS # 25339-17-7), alcohols, C7-9-iso-, C8-rich (CAS # 68526-83-0), 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 alcohols, C11-14-iso-, C13-rich (CAS # 68526-86-3), isodecyl alcohol (CAS # 25339-17-7) can be used as a structurally similar read-across analog for the genotoxicity endpoint, alcohols, C7-9-iso-, C8-rich (CAS # 68526-83-0) can be used as a structurally similar read-across analog for the developmental and reproductive toxicity endpoint, and isoamyl alcohol (CAS # 123-51-3) and isononyl alcohol (CAS # 27458-94-2) can be used as a structurally similar read-across analogs for the skin sensitization endpoint.
  - o The target substance and the read-across analogs are structurally similar and belong to a class of saturated branched chain aliphatic primary alcohols.
  - o The key difference between the target substance and the read-across analogs is that they have different aliphatic carbon chain lengths. This structural difference between the target substance and read-across analogs is not relevant from a toxicity endpoint perspective.
  - o The target substance and the read-across analogs have a Tanimoto score as mentioned in the table above. The Tanimoto score is mainly driven by the five carbon long branched aliphatic chain fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicological perspective.
  - o The target substance and the read-across analog 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 either up to 40% or 80%. Other differences in some of the physical-chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant.
  - o 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.
  - o 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 a comparison of structure similarity, physical-chemical properties and reactivity predictions between the read-across analogs and the target substance, the alert for the target was superseded by availability of data for the read-across analog(s). In addition, according to the CAESAR model, the read-across analogs are predicted to be toxicants with good reliability for the developmental and reproductive toxicity endpoint. The data described above in the developmental and reproductive 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 was superseded.
  - o The target substance and the read-across analogs are expected to be metabolized similarly as shown by metabolism simulator.
  - o The structural alerts for the respective toxicological endpoints are consistent between the metabolites of the read-across analog(s) and the target substance.
  - o 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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