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Short review

RIFM fragrance ingredient safety assessment, dihydro-β-ionol, cas registry number 3293-47-8

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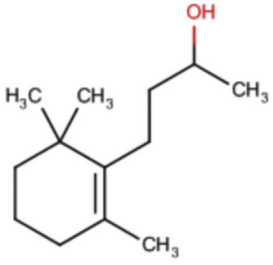
Name: Dihydro-β-ionol
CAS Registry Number: 3293-47-8



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

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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 toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) show that this material is not genotoxic and provided a MOE > 100 for the repeated dose, developmental and reproductive toxicity endpoints. Target data indicate that this material does not present a skin sensitization concern. 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 # 3293-47-8 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, 2007; RIFM, 2014a)

Repeated Dose Toxicity: NOAEL = 300 mg/kg/day (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol)

Developmental and Reproductive Toxicity: NOAEL = 100 mg/kg/day and 300 mg/kg/day, respectively.(ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol).

Skin Sensitization: Not a sensitization concern. (RIFM, 1996)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening Level: 2.71 (Biowin 3) (EpiSuite ver 4.1)

Bioaccumulation: Screening Level: 749 L/kg (EpiSuite ver 4.1)

Ecotoxicity: Screening Level: 48 h *Daphnia magna* LC50: 0.321 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 (Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* LC50: 0.321 mg/L (EpiSuite ver 4.1)

RIFM PNEC is: 0.0321 μg/L

•Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe: < 1

1. Identification

1. **Chemical Name:** Dihydro-β-ionol
2. **CAS Registry Number:** 3293-47-8
3. **Synonyms:** 1-Cyclohexene-1-propanol,.α.,2,6,6-tetramethyl-; Dihydro-β-ionol; β-Dihydroionol; a,2,6,6-Tetramethylcyclohexene-1-propan-1-ol; 4-(2,6,6-Trimethyl-1-cyclohexenyl)butan-2-ol; 4-(2,6,6-ﾄﾘﾒﾁﾙ-1-ｼｸﾛﾍｷｾﾆﾙ)q-2-ﾌﾞﾀﾉｰﾙ; 4-(2,6,6-Trimethylcyclohex-1-en-1-yl)butan-2-ol
4. **Molecular Formula:** $C_{13}H_{24}O$
5. **Molecular Weight:** 196.33
6. **RIFM Number:** 5091

2. Physical data

1. **Boiling Point:** 272.16 °C [EPI Suite]
2. **Flash Point:** > 93 °C [GHS]
3. **Log K_{OW}:** 4.86 [EPI Suite]
4. **Melting Point**: 55.63 °C [EPI Suite]
5. **Water Solubility:** 10.43 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000207 mmHg @ 20 °C [EPI Suite 4.0], 0.000412 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0095% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000031 mg/kg/day or 0.0023 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00030 mg/kg/day (RIFM, 2016)

*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 IV. 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).

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)

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

*See Appendix below for explanation.

6. Analogs selected

a. **Genotoxicity:** 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
b. **Repeated Dose Toxicity:** 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
c. **Developmental and Reproductive Toxicity:** 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

7. Metabolism

There are no metabolism data on dihydro-β-ionol and hence not considered for this risk assessment.

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

Dihydro-β-ionol is reported to occur in the following foods* and in some natural complex substances (NCS):

Chinese quince (Pseudocydonia sinensis Schneid)
Loganberry (Rubus ursinus var. loganobaccus)
Quince, Marmelo (Cydonia oblonga Mill.)

*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.

9. IFRA standard

None.

10. REACH dossier

Pre-registered for 2010, no dossier available as of 04/20/2017.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, dihydro-β-ionol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Dihydro-β-ionol was assessed in the BlueScreen assay and found negative for both genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). There are no studies assessing the mutagenic activity of dihydro-β-ionol however, read across can be made to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section V). The mutagenicity of read across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol 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, TA98, and TA100 and *Escherichia coli* strain WP2uvrA were exposed to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2007). These results indicate that 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is non-mutagenic in the Ames test when tested up to 5000 μg/plate under the conditions of the study.

There are no studies assessing the clastogenic activity of dihydro-β-ionol however, read across can be made to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section V). The clastogenicity of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol 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 fibroblasts were exposed to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in DMSO at concentrations up to 190 μg/mL in the presence and absence of exogenous metabolically active microsomal mixture. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration, either with or without metabolic activation (RIFM, 2014a). Under the conditions of the study, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol does not present a concern for genotoxic potential and this can be extended to dihydro-β-ionol.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/14/2016.

11.1.2. Repeated dose toxicity

The margin of exposure for dihydro-β-ionol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on dihydro-β-ionol. Read across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section V), has sufficient repeated dose toxicity data. A 28-day repeated-dose oral toxicity study was conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (bacdanol). Groups of 5 Crl:CD(SD) rats/sex/dose were administered via gavage test material at dose levels of 0, 100, 350 and 1000 mg/kg/day dissolved in corn oil for 28 days. Controls and high dose recovery groups were set for the control and 1000 mg/kg/day groups to investigate the reversibility of treatment effects for 14 days. Effects on the liver and kidneys and irritating effects on the digestive tracts such as the forestomach attributable to the test substance were detected but

only at the highest dose tested. Microscopic alterations included test material-related alterations in the hepatocytes and kidney tubules as well as the stomach. All these effects were seen to be reversible, except for incidences of granulomas of the female hepatocytes. Hence, the NOAEL was determined to be 350 mg/kg/day (RIFM, 2014b). In another OECD 422 GLP study conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol, there were 3 treatment groups, The toxicity subgroup (Toxicity phase): 10 males and 5 females/dose (except for control males and at top dose: 5 males/dose), the Reproductive subgroup (Main Phase): 10 females/dose and same males as for toxicity subgroup and the Recovery subgroup: 5 males and 5 females/dose (control and top dose). Recovery phase males were also used for pairing with Main reproductive phase females. The animals received test material at doses of 0, 100, 300 or 1000 mg/kg/day in corn oil. Mortality was reported among the high dose group females and typical terminal clinical signs were reported among these females. Lower food consumption and body weight gains were reported among high dose females. Kidney and liver weights were increased among high dose females. No such effects persisted among the recovery group animals. Microscopic findings included centrilobular hepatocytes enlargement among females. These effects were not observed among the recovery group animals. No adverse effects were reported among the low- and mid-dose group animals. Thus, the NOAEL for the male and female systemic toxicity was determined to be 300 mg/kg/day due to mortality and clinical conditions reported among high dose females (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). In another study, test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was administered to 10 Crl:CD(SD) rats/sex/dose at doses of 0, 1500, 5000 or 15000 ppm (equivalent to 100, 330 and 981 mg/kg/day for males and 109, 362 and 1109 mg/kg/day for females, respectively, according to body weight and food consumption parameters). An additional group of 5 male and 5 female rats were assigned to the control and high dose groups. The study was conducted according to the OECD 408 protocol. Reduced food consumption, with associated reductions in body weight gain was evident in the 15000 ppm group, however this was attributed to the treated diet being unpalatable due to the high concentration of test material, but not adverse effect due to treatment with test material. Alteration in hematological parameters were reported but were not considered to be due to treatment with test material. Organ weights analysis indicated dose-dependent and statistically significantly higher than the control body weight-adjusted liver weights in all groups of treated males and in females administered 5000 or 15000 ppm of test material. Relative kidney weights were higher than the control in females given 15000 ppm, and body weight-adjusted uterus and cervix weights were slightly lower in females given 5000 or 15000 ppm. Following 4 weeks of recovery, relative liver weights in males previously given 15000 ppm remained slightly higher than the control, although the magnitude of the difference was lower than that recorded at the end of the treatment period. Plasma biochemistry revealed several slight changes in composition which were indicative of adaptations of metabolism/excretion in the liver and kidneys, and were accompanied by increases in liver and kidney weight. Under the conditions of this study, there was clear evidence of systemic exposure but no effects were deemed to be adverse. Thus, the NOAEL was determined to be 15000 ppm, equivalent to 981 mg/kg/day for males and 1109 mg/kg/day for females the highest dose tested (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). The most conservative NOAEL of 300 mg/kg/day from the 28-day study was selected for the repeated dose toxicity endpoint. Since there was a 13-week dietary study on the same chemical indicating a higher NOAEL, the safety factor was not included to derive a NOAEL from the 28-day study. **Therefore, the dihydro-β-ionol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to dihydro-β-ionol, 300/0.0003 or 1000000.**

In addition, the total systemic exposure to dihydro-β-ionol (0.3 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: None.

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

11.1.3. Developmental and reproductive toxicity

The margin of exposure for dihydro-β-ionol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on dihydro-β-ionol. Read across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section V) have sufficient developmental toxicity data. An OECD 414 GLP prenatal developmental toxicity study was conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. Groups of mated female Crl:CD(SD) rats (20/dose) were gavaged with test material at dose levels of 0, 100, 300 and 750 mg/kg/day in corn oil from days 6–19 after mating. Maternal weight gain during gestation and uterine weights were lower among the high dose females as compared to the control. The mean fetal weights were lower than the control for the 300 and 750 mg/kg/day dose groups. This was considered to be due to maternal toxicity and not considered to be a developmental toxicity adverse effect. Incidences of skeletal variations and ossifications were observed among the pups of the treated animals, however this was again considered to be due to maternal toxicity and not considered to be an adverse developmental toxic effect due to test material administration. Thus, the most conservative NOAEL for developmental toxicity was determined to be 100 mg/kg/day, based on decrease in mean fetal weights among higher dose group animals (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). **Therefore, the dihydro-β-ionol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to dihydro-β-ionol, 100/0.0003 mg/kg/day or 333333.**

There are no reproductive toxicity data on dihydro-β-ionol. Read across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section V), has sufficient reproductive toxicity data. An OECD 422 GLP study was conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. There were 3 treatment groups, the **Toxicity subgroup (Toxicity phase):** 10 males and 5 females/dose (except for control males and at top dose: 5 males/dose), the **Reproductive subgroup (Main Phase):** 10 females/dose and same males as for toxicity subgroup and the **Recovery subgroup:** 5 males and 5 females/dose (control and top dose). Recovery phase males were also used for pairing with Main reproductive phase females. There were no adverse effects in the male and female reproductive organs up to the highest dose tested. However, mortality was reported among animals of the high dose group. Thus, the NOAEL for the reproductive toxicity endpoint was considered to be 300 mg/kg/day (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). **Therefore, the dihydro-β-ionol MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to dihydro-β-ionol, 300/0.0003 mg/kg/day or 1000000.**

In addition, the total systemic exposure to dihydro-β-ionol (0.3 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 Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol.

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

11.1.4. Skin sensitization

Based on the existing data, dihydro-β-ionol does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, dihydro-β-ionol does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a guinea pig maximization test, dihydro-β-ionol did not result in sensitization (RIFM, 1996). Based on the weight of evidence from structural analysis and animal data, dihydro-β-ionol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/12/2016.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, dihydro-β-ionol 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 dihydro-β-ionol 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on the lack of absorbance, dihydro-β-ionol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/07/2016.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, dihydro-β-ionol, exposure level 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 dihydro-β-ionol. Based on the Creme RIFM model, the inhalation exposure is 0.0023 mg/day. This exposure is 609 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: 10/20/2016.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening level risk assessment of dihydro-β-ionol 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, which is considered proprietary information, 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, dihydro-β-ionol 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 dihydro-β-ionol 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2011), dihydro-β-ionol presents a risk to the aquatic compartment in the screening level assessment.

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. Dihydro-β-ionol has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>0.8605 mg/L</u>			1,000,000	0.000861 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.434 mg/L	<u>0.321 mg/L</u>	0.713 mg/L	10,000	0.0312 μg/L	Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.86	4.86
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
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 0.0321 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: 09/13/2016.

12. 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=KMSoUpiQKarsQS324GwBg&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.2017.10.010.

Transparency document

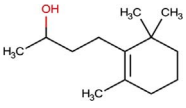
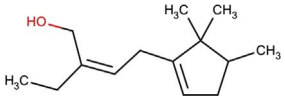
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.010.

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)

	Target material	Read across material
Principal Name	Dihydro-beta-ionol	2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol
CAS No.	3293-47-8	28219-61-6
Structure		
Similarity (Tanimoto score)[1]		0.712
Read across endpoint		• Developmental and Reproductive • Genotoxicity •Repeated dose
Molecular Formula	$C_{13}H_{24}O$	$C_{14}H_{24}O$
Molecular Weight	196.33	208.35
Melting Point (°C, EPISUITE)	55.63	60.19

Boiling Point (°C, EPISUITE)	272.16	298.07
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.055	0.00958
Log Kow (KOWWIN v1.68 in EPISUITE)	4.86	4.4[1]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	10.43	5.256
J_{max} (mg/cm^2/h, SAM)	40.78	10.985
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.36E-005	5.09E-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 (moderate 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 without OH or NH_2 group	• Non binder without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• toxicant (good reliability)	• toxicant (low reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

1. RIFM, 2004.

Summary

There are insufficient toxicity data on dihydro-beta-ionol (CAS # 3293-47-8). Hence, *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, analog 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) was identified as a proper read across material with data for its respective toxicity endpoints.

Conclusion/Rational

- 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) could be used as structurally similar read across analog for target material dihydro-beta-ionol (CAS # 3293-47-8) for genetoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints.
  - The target sunstance and the read across analog are structurally similar and belongs to a class of unsaturated clcylc terpene alcohols.
  - The target sunstance and the read across analog have a vinylene containing 2,2-dimethyl substituted cyclic ring structure common among them.
  - The key difference between the target substance and the read across analog is that the target substance is a cylcohexene ring with a butanol substituent at the alpha position and it is a secondary alcohol, while the read across analog is a cyclopentene ring with a buten-1-ol substituent at the alpha position and it has alpha-beta unsaturaiton.
  - 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 vinylene containing 2,2-dimethyl substituted cyclic fragment. The differences in the structure which are responsible for Tanimoto score < 1 are not relevant from a toxicicological perspective.
  - The target substance and the read across analog have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints are consistent between the target substance and the read across analog.
  - According to CAESAR model, both, the read across analog and the target substance are predicted to be toxicants for developmental toxicity endpoint. The data described in the developmental toxicity section above describes that the read across substance pose no concern. Therefore, the alert will be superseded by the availability of data.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - The structural alerts for the genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read across analog and the target substance.
  - The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant for genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints.

Explanation of Cramer Class: 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 (see Cramer et al., 1978 for explanation) **No**
Q17. Readily hydrolysed to a common terpene **No**
Q19. Open chain **No**
Q23. Aromatic **No**
Q24. Monocarbocyclic with simple substituents **Yes**
Q18. One of the list (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)**No** Class Low (Class I)

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