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Short Review

RIFM fragrance ingredient safety assessment, cyclopentanol, 2-(2-hexen-1-yl)-, CAS Registry Number 34686-67-4

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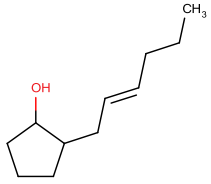

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

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

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

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

Cyclopentanol, 2-(2-hexen-1-yl)- (CAS # 34686-67-4) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclopentanol, 2-(2-hexen-1-yl)- is not genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. Data from read-across analog *cis*-jasmone (CAS # 488-10-8) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to cyclopentanol, 2-(2-hexen-1-yl)- is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; cyclopentanol, 2-(2-hexen-1-yl)- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cyclopentanol, 2-(2-hexen-1-yl)- was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2017b; RIFM, 2017c)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day. RIFM (2015)
Reproductive Toxicity: Developmental toxicity NOAEL = 250 mg/kg/day. Fertility NOAEL = 750 mg/kg/day. RIFM (2015)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be 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: 3.3 (BIOWIN 3) (US EPA, 2012a)
Bioaccumulation: Screening-level: 150.3 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 68.50 mg/L (RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 68.50 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.06850 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Cyclopentanol, 2-(2-hexen-1-yl)-
2. **CAS Registry Number:** 34686-67-4
3. **Synonyms:** Jasmonol 406; Cyclopentanol, 2-(2-hexen-1-yl)-
4. **Molecular Formula:** $C_{11}H_{20}O$
5. **Molecular Weight:** 168.28

6. **RIFM Number:** 6966
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 8 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 257.07 °C (US EPA, 2012a)
2. **Flash Point:** 200.00 °F. TCC (93.33 °C)*
3. **Log K_{OW}:** 3.8 (US EPA, 2012a)
4. **Melting Point:** 19.71 °C (US EPA, 2012a)
5. **Water Solubility:** 114.3 mg/L (US EPA, 2012a)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00117 mm Hg @ 20 °C (US EPA, 2012a v4.0), 0.00206 mm Hg @ 25 °C (US EPA, 2012a)
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:** Colorless, clear liquid; floral, green, fruity, natural, waxy, jasmin, tropical, banana*

* http://www.thegoodscentscompany.com/data/rw1000341.html, retrieved 12/5/2017.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.004% (RIFM, 2017a)
3. **Inhalation Exposure*:** 0.0000014 mg/kg/day or 0.00010 mg/day (RIFM, 2017a)
4. **Total Systemic Exposure**:** 0.000060 mg/kg/day (RIFM, 2017a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey 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., 2015a; Safford et al., 2017; and Comiskey 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 v2.6	OECD QSAR Toolbox v3.2
I*	II	I

*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). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** *cis*-Jasmone (CAS # 488-10-8)
   c. **Reproductive Toxicity:** *cis*-Jasmone (CAS # 488-10-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Cyclopentanol, 2-(2-hexen-1-yl)- is not reported to occur in food by the VCF.*

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 05/31/2018; no dossier available as of 08/03/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, cyclopentanol, 2-(2-hexen-1-yl)- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Cyclopentanol, 2-(2-hexen-1-yl)- was assessed in the BlueScreen assay and found negative for both cytotoxicity (reduced the relative cell density to less than 80%) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a screening assay, which assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

The mutagenic activity of cyclopentanol, 2-(2-hexen-1-yl)- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with cyclopentanol, 2-(2-hexen-1-yl)- in solvent dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017b). Under the conditions of the study, cyclopentanol, 2-(2-hexen-1-yl)- was not mutagenic in the Ames test.

The clastogenic activity of cyclopentanol, 2-(2-hexen-1-yl)- was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with cyclopentanol, 2-(2-hexen-1-yl)- in DMSO at concentrations up to 1000 µg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Cyclopentanol, 2-(2-hexen-1-yl)-

did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either non-activated or S9-activated test systems (RIFM, 2017c). Under the conditions of the study, cyclopentanol, 2-(2-hexen-1-yl)- was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, cyclopentanol, 2-(2-hexen-1-yl)- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/02/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for cyclopentanol, 2-(2-hexen-1-yl)- 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 cyclopentanol, 2-(2-hexen-1-yl)-. Read-across material *cis*-jasmone (CAS # 488-10-8) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. A dietary OECD 422 combined repeated dose toxicity with a reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing test material *cis*-jasmone at doses of 0 (basic powdered diet), 1500, 5000, or 15000 ppm (equivalent to 0, 75, 250, or 750 mg/kg/day, as per the conversion factors for old rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The animals were treated for 14 days before mating, throughout mating (total of 28 days for males), throughout gestation, and until day 4 postpartum for the females. There was an overall statistically significant reduction in the terminal body weight for males at 5000 ppm (−8%) and at 15000 ppm (−18% and −17% for males and females, respectively). The reduction in bodyweight gain was correlated with decreases in food consumption. There was an increase in the absolute and relative liver weights of all treated males and mid- and high-dose females, often reaching statistical significance. Hepatocyte hypertrophy of the liver was observed histopathologically in 4 mid-dose females and 7 high-dose (male and female) group animals. The liver weight increases were considered to be adaptive since there was no evidence of liver cell damage and clinical chemistry alterations (Hall et al., 2012). The relative kidney weight was statistically significantly increased in 15000 ppm males. The kidney of males at 5000 ppm (3/5) and 15000 ppm (all males) exhibited cortical tubular degeneration or regeneration. These kidney changes in males were confirmed with Martius Scarlet Blue staining and were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). There was a decrease in the absolute and relative thymus weights in males and females at 15000 ppm, which reached statistical significance for the females. This finding correlated with atrophy seen in 1 male and 3 females at 15000 ppm. This was considered likely to be a secondary effect due to bodyweight loss seen at this dose. In the spleen, extramedullary hematopoiesis was increased in all treatment groups except for females at 15000 ppm, which correlated with a statistically significant decrease in spleen weight in females at this dose only. The absolute and relative adrenal weights were lower than the controls at 5000 and 15000 ppm in females, with no histopathological correlates. However, minimal or slight zona fasciculata vacuolation was observed in 4 of the 5 males at 15000 ppm. The NOAEL was considered to be 1500 ppm or 75 mg/kg/day, based on a statistically significant reduction in the terminal body weight of males and females in the higher dose groups and a decrease in the adrenal weights of females in the higher dose group (RIFM, 2015). A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 75/3 or 25 mg/kg/day.

Therefore, the cyclopentanol, 2-(2-hexen-1-yl)- MOE for the repeated dose toxicity endpoint can be calculated by dividing the cis-jasmone NOAEL in mg/kg/day by the total systemic exposure to cyclopentanol, 2-(2-hexen-1-yl)-, 25/0.00006 or 416667.

In addition, the total systemic exposure to cyclopentanol, 2-(2-hexen-1-yl)- (0.06 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.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/17.

10.1.3. Reproductive toxicity

The margin of exposure for cyclopentanol, 2-(2-hexen-1-yl)- is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on cyclopentanol, 2-(2-hexen-1-yl)-. Read-across material *cis*-jasmone (CAS # 488-10-8) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. A dietary OECD 422 combined repeated dose toxicity with a reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing test material *cis*-jasmone at doses of 0 (basic powdered diet), 1500, 5000, or 15000 ppm (equivalent to 0, 75, 250, or 750 mg/kg/day, as per the conversion factors for old rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The animals were treated for 14 days before mating, throughout mating (total of 28 days for males), throughout gestation, and until day 4 postpartum for the females. In addition to the systemic toxicity parameters, the developmental (number of pups born, pup survival, sex ratio, and pup weights) and reproductive (evaluation of the testes, spermatogenic and estrous cycles) parameters were also assessed. Three females given 15000 ppm were euthanized following total litter loss postpartum. However, no treatment-related histopathological findings in the reproductive organs were observed from the 3 dams that could have caused the loss of the litters. At 15000 ppm, a treatment-related postnatal effect was observed on pup survival and growth. The viability index of pups at PND 4 was significantly lower (69.9%) than in the control (100%) and the historical control data range (94.1–100%) due to the 3 dams with total litter loss between PND 1–4. The terminal mean pup weight at PND 4 was statistically significantly decreased (−17%) when compared to the controls. The NOAEL for developmental toxicity was considered to be 5000 ppm or 250 mg/kg/day, based on treatment-related effects on early postnatal development (pup mortality and reduced pup weight) in the 15000 ppm group, which were consistent with the severity of the maternal toxicity observed in the high-dose group. There were no treatment-related effects on mating performance and fertility up to the highest dose group tested. Thus the NOAEL for fertility was considered to be 15000 ppm, or 750 mg/kg/day, the highest dose tested (RIFM, 2015).

Therefore, the cyclopentanol, 2-(2-hexen-1-yl)- MOE for the developmental toxicity endpoint can be calculated by dividing the cis-jasmone NOAEL in mg/kg/day by the total systemic exposure to cyclopentanol, 2-(2-hexen-1-yl)-, 250/0.00006 or 4166667.

Therefore, the cyclopentanol, 2-(2-hexen-1-yl)- MOE for the fertility endpoint can be calculated by dividing the cis-jasmone NOAEL in mg/kg/day by the total systemic exposure to cyclopentanol, 2-(2-hexen-1-yl)-, 750/0.00006 or 12500000.

In addition, the total systemic exposure to cyclopentanol, 2-(2-

Table 1
Acceptable concentrations for cyclopentanol, 2-(2-hexen-1-yl)- that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products Based on Non-reactive DST	95th Percentile Concentration in Finished Products
1	Products applied to the lips	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%
10	Household care products with mostly hand contact	2.70%	0.00%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00%[b]

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

hexen-1-yl)- (0.06 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/17.

10.1.4. Skin sensitization

Based on the application of DST, cyclopentanol, 2-(2-hexen-1-yl)- does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). No skin sensitization studies are available for cyclopentanol, 2-(2-hexen-1-yl)- or for a suitable read-across. Acting conservatively, due to insufficient data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 Safford (2008); Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentrations for cyclopentanol, 2-(2-hexen-1-yl)- that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/18/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cyclopentanol, 2-(2-hexen-1-yl)- 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 cyclopentanol, 2-(2-hexen-1-yl)- in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, cyclopentanol, 2-(2-hexen-1-yl)- does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/11/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for cyclopentanol, 2-(2-hexen-1-yl)- 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 cyclopentanol, 2-(2-hexen-1-yl)-. Based on the Creme RIFM Model, the inhalation exposure is 0.00010 mg/day. This exposure is 14000 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: 11/30/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of cyclopentanol, 2-(2-hexen-1-yl)- was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity

estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify clyclopentanol, 2-(2-hexen-1-yl)- as possibly persistent or bioaccumulative based on its structure and physical–-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), clyclopentanol, 2-(2-hexen-1-yl)- does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Cyclopentanol, 2-(2-hexen-1-yl)- has been pre-registered for REACH with no additional data at this time.

10.2.3. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	68.50			1,000,000	0.06850	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.8	3.8
Biodegradation Factor Used	0	0
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 further assessment is necessary.

The RIFM PNEC is 0.06850 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level 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: 11/20/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **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://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 06/12/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.05.044.

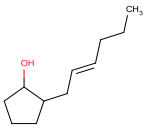
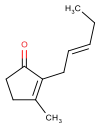
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted 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	Cyclopentanol, 2-(2-hexen-1-yl)-	*cis*-Jasmone
CAS No.	34686-67-4	488-10-8
Structure		
Similarity (Tanimoto Score)		0.77
Read-across Endpoint		• Repeated dose • Reproductive
Molecular Formula	$C_{11}H_{20}O$	$C_{11}H_{16}O$
Molecular Weight	168.28	164.25
Melting Point (°C, EPI Suite)	19.71	40.24
Boiling Point (°C, EPI Suite)	257.07	256.01
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.274	59.7
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.8	2.8[1]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	114.3	60.54
J_{max} (μg/cm^2/h, SAM)	37.498	54.602
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.78E-005	1.21E-004
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	• Weak binder OH group	• Non-binder without OH and NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (low reliability)	• Toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

1. RIFM, 1998.

Summary

There are insufficient toxicity data on cyclopentanol, 2-(2-hexen-1-yl)- (CAS # 34686-67-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, *cis*-jasmone (CAS # 488-10-8) was identified as read-across material with sufficient data for toxicological evaluation.

Conclusions

- *cis*-Jasmone (CAS # 488-10-8) was used as a read-across analog for the target material cyclopentanol, 2-(2-hexen-1-yl)- (CAS # 34686-67-4) for the repeated dose and reproductive toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the classes of cyclic aliphatic alcohols and ketones, respectively.
  - o The target substance and the read-across analog share an unsaturated alkyl cyclopentyl structure.
  - o The key structural difference between the target substance and the read-across analog is the target substance is a cyclopentyl alcohol while the read-across analog is a methyl cyclopentyl ketone. The unsaturated alkyl chains differ in length by one carbon. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly

driven by the common unsaturated alkyl cyclic fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o According to the CAESAR model, the target material and the read-across analog are predicted to be toxicants; in addition, the target material is also predicted to be a weak binder. The predictions are superseded by data.
- o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

Q1. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene (see explanation in Cramer et al., 1978)? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **Yes**
Q18. One of the following category? (a) a vicinal diketone, or a ketone or ketal of a ketone attached to a terminal vinyl group; (b) a secondary alcohol or ester of a secondary alcohol attached to a terminal vinyl group; (c) allyl alcohol or its acetal, ketal, or ester derivative; (d) allyl mercaptan, an allyl sulphide, an allyl thioester or allyl amine; (e) acrolein, a methacrolein, or ther acetals; (f) acrylic or methacrylic acid; (g) an acetylenic compound; (h) an acyclic aliphatic ketone, ketal, or ketoalcohol with no other functional groups and with 4 or more carbons on either side of the keto group; (i) a substance in which the functional groups are all sterically hindered (see Cramer et al., 1978 for detailed explanation)? **No, Low Class I**

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