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Short review

RIFM fragrance ingredient safety assessment, *cis*-4-(isopropyl) cyclohexanemethanol, CAS Registry Number 13828-37-0

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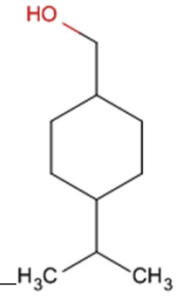
Version: 060519. This version replaces any previous versions.



Name: *cis*-4-(Isopropyl)cyclohexanemethanol
CAS Registry Number: 13828-37-0

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

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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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose range finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api 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.

cis-4-(Isopropyl)cyclohexanemethanol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *cis*-4-(isopropyl)cyclohexanemethanol is not genotoxic. Data on *cis*-4-(isopropyl)cyclohexanemethanol provided a calculated margin of exposure (MOE) $>$ 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. Data provided *cis*-4-(isopropyl)cyclohexanemethanol a No Expected Sensitization Induction Level (NESIL) of 17000 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to *cis*-4-(isopropyl)cyclohexanemethanol is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra. The environmental endpoints were evaluated; *cis*-4-(isopropyl)cyclohexanemethanol was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., predicted environmental concentration/predicted no effect concentration [PEC/PNEC]), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2004b; RIFM, 2012d)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day. RIFM, (2013c)
Developmental and Reproductive Toxicity: NOAEL = 50 mg/kg/day and 150 mg/kg/day, respectively. RIFM, (2013d)
Skin Sensitization: NESIL = 17000 μg/cm^2. (RIFM, 2005; RIFM, 2012c)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 74% (OECD 301F) RIFM, (2012g)
Bioaccumulation: Screening-level: 88.39 L/kg (EPI Suite, v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 4.117 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) $>$ 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 4.117 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.4117 μg/L

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

1. Identification

1. **Chemical Name:** *cis*-4-(Isopropyl)cyclohexanemethanol
2. **CAS Registry Number:** 13828-37-0
3. **Synonyms:** Cyclohexanemethanol, 4-(1-methylethyl)-, *cis*; Mayol; *cis-p*-Menthan-7-ol; ハßラ-メンタン-7-オール; Meijiff; (4-Isopropylcyclohexyl) methanol; Reaction mass of *trans*-4-(isopropyl)cyclohexanemethanol and *cis*-4-(isopropyl)cyclohexanemethanol; *cis*-4-(Isopropyl)cyclohexanemethanol
4. **Molecular Formula:** $C_{10}H_{20}O$
5. **Molecular Weight:** 156.26
6. **RIFM Number:** 1324

2. Physical data

1. **Boiling Point:** 505 +/-2K (232 +/-2 °C) at 97.1 kPa (RIFM, 2004a), 231 °C at 1013 hPa (T corrected) (RIFM, 2011c), 115 °C (RIFM, 1981), 230.44 °C (EPI Suite)
2. **Flash Point:** 109 +/-2 °C (RIFM, 2004a), pH 4, pH 7, pH 9, est. 1/2 life @ 25 °C = > 1 year (RIFM, 2012b)
3. **Log K_{OW}:** 3.02 x 10(3), log10 Pow = 3.48 (RIFM, 2011d), 3.45 (EPI Suite)
4. **Melting Point**: less than 253 +/-0.5K (< -20 +/-0.5 °C) (RIFM, 2004a), −0.42 °C (EPI Suite)
5. **Water Solubility:** 213.7 mg/L at 20 +/-0.5 °C (RIFM, 2011b), 258.2 mg/L (EPI Suite)
6. **Specific Gravity:** 0.910–0.916 (RIFM, 1981)
7. **Vapor Pressure:** 0.022496 hPa @ 25 °C (RIFM, 2011a), 0.0338 torr (Vuilleumier et al., 1995), 0.00672 mm Hg @ 20 °C (EPI Suite v4.0), 0.004 mm Hg 20 °C (FMA; calculated), 0.0113 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a medium, fresh, clean, floral, magnolia hydroxycitronellal, cumin, and grassy odor

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.38% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00080 mg/kg/day or 0.058 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0091 mg/kg/day (RIFM, 2016)

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

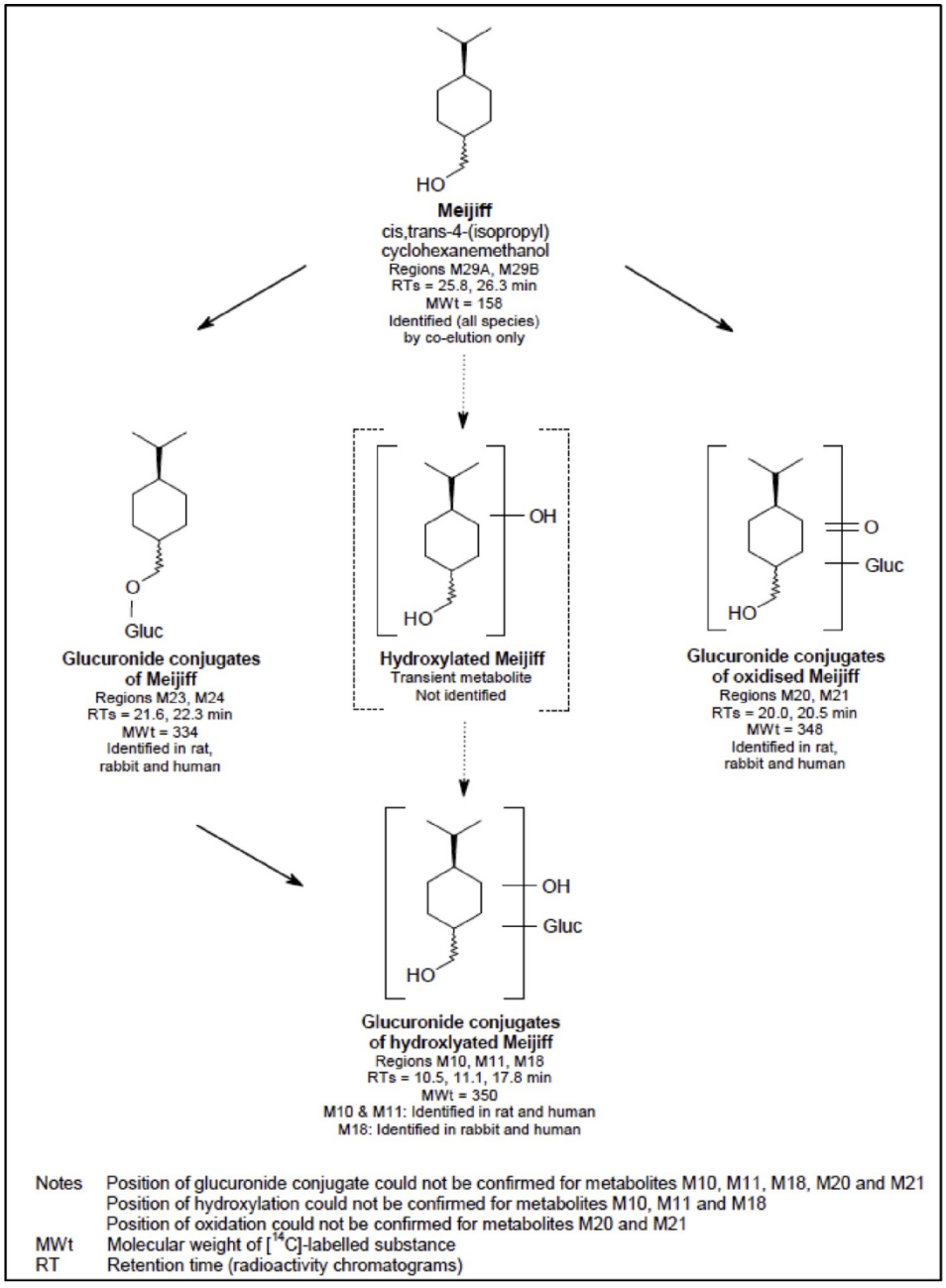
1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

6. Metabolism

RIFM, 2014b**:** The primary objective of this study was to compare the *in vitro* metabolism of test material, [^{14}C]-*cis*,*trans*-4-(isopropyl)cyclohexanemethanol (Meijiff) between 3 species (rat, rabbit, and human) using hepatocytes. The analytical method utilized radio-HPLC to determine metabolite profiles, followed by HPLC coupled with mass spectrometry (LC-MS) to identify the radiolabeled metabolites generated. The test material was incubated in triplicates with cryopreserved hepatocytes from rats, rabbits, and humans at concentrations of 1, 10, and 100 μM, over incubation times of 0, 1, and 4 h, respectively. At the end of the incubation period, the experiment was terminated, and the samples were collected for analysis by LC-MS to identify the principle metabolites observed. The viability and cellular integrity were also monitored independently along with the inclusion of a positive control, 7-ethoxy[^{14}C]coumarin (7-EC). All of the results obtained from the characterization of the isolated hepatocytes for each species showed that the cells were metabolically viable over the incubation periods used in this study. Loss of radioactivity with the test material was limited to only the rapid and extensive metabolism and not the evaporative loss. The metabolism of the test material, during incubation with rat, rabbit, and human hepatocytes was both rapid and extensive. Up to 31 individual regions of radioactivity were observed, which included a pair of regions (M29A and M29B) attributed to the 2 isomers of the unchanged test material, although it was not possible to confirm their identities by LC-MS. A metabolism pathway was proposed for the test material, and the components that were identified by LC-MS were regions M10, M11, and M18 (glucuronide conjugates of hydroxylated Meijiff), regions M20 and M21 (glucuronide conjugates of oxidized Meijiff), and regions M23 and M24 (glucuronide conjugates of Meijiff). Additional components that were considered major in at least one profile were M1, M2, M12, and M28, although the identities of these could not be derived.



Following 4-h incubation periods of the test material in the absence of hepatocytes, the percentage of sample radioactivity in each region in the profiles contained unresolved regions M29A and M29B attributed to the unchanged test material. 34%–96% of unchanged test material was recovered after incubation for 4 h without hepatocytes at concentrations ranging from 1 to 100 μM. The following table shows the metabolites reported with their respective percentages. Overall, the Meijiff metabolism profile for hepatocytes from rats, rabbits, and humans was not different.

Regions	Identity	Rat			Rabbit			Human		
		1 μM	10 μM	100 μM	1 μM	10 μM	100 μM	1 μM	10 μM	100 μM
M1	Not Identified	Minor	Minor	Minor	Minor	13.40%	Minor	Minor	13.40%	Minor
M2	Not Identified	Minor	Minor	Minor	Minor	Minor	Minor	Minor	12.10%	Minor
M10	Gluc-OH-Meijiff	–	Minor	Minor	35.30%	Minor	Minor	25.70%	Minor	Minor
M11		–	Minor	Minor	–	12.50%	12.50%	–	17.40%	17.40%
M12	Not Identified	Minor	Minor	10.10%	14.10%	12.80%	Minor	Minor	Minor	Minor
M20 and M21	Gluc-Oxidized-Meijiff	–	Minor	Minor	–	Minor	Minor	–	Minor	Minor
M23	Gluc-Meijiff (Hydroxy Group Conjugation)	–	34.80%	29.80%	Minor	Minor	Minor	–	10.80%	11%
M24		Minor	Minor	Minor	Minor	Minor	Minor	Minor	Minor	Minor
M28	Not Identified	–	–	–	Minor	Minor	48.60%	Minor	Minor	30.10%
M29A and M29B	Unchanged Meijiff	–	–	Minor	–	–	Minor	–	–	Minor

Minor: 0.5%–10% of sample radioactivity.
-: Unresolved.

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

cis-4-(Isopropyl)cyclohexanemethanol is reported to occur in the following foods by the VCF*:

Mentha oils.

*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. REACH dossier

cis-4-(Isopropyl) cyclohexanemethanol has been pre-registered for 2010; no dossier available as of 04/23/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for *cis*-4-(isopropyl)cyclohexanemethanol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.25
2	Products applied to the axillae	0.39
3	Products applied to the face/body using fingertips	0.099
4	Products related to fine fragrances	4.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.2
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.15
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.20
5D	Baby cream, oil, talc	0.049
6	Products with oral and lip exposure	0.0099
7	Products applied to the hair with some hand contact	0.13
8	Products with significant ano-genital exposure (tampon)	0.049
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.39
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.39
10B	Aerosol air freshener	1.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.049
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	28

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For *cis*-4-(isopropyl)cyclohexanemethanol, the basis was the reference dose of 0.5 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 17000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, *cis*-4-(isopropyl)cyclohexanemethanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. *cis*-4-(Isopropyl)cyclohexanemethanol was tested in the BlueScreen assay and found negative for genotoxicity with or without metabolic activation, indicating a lack of genotoxic concern RIFM, 2013a). The mutagenic activity of *cis*-4-(isopropyl) cyclohexanemethanol has been assessed in an Ames assay in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and *Escherichia coli* strain WP2 uvrA were treated with *cis*-4-(isopropyl) cyclohexanemethanol in dimethyl sulfoxide (DMSO) at the concentrations 5, 15, 50, 150, 500, and 1500 μg/plate in the presence and absence of S9 mix. No increase in the number of revertant colonies was observed in any of the tester strains at any of the concentrations assessed (RIFM, 2004b). Under the conditions of the study, *cis*-4-(isopropyl)cyclohexanemethanol was not considered to be mutagenic in the Ames test.

The clastogenic potential of *cis*-4-(isopropyl)cyclohexanemethanol has been assessed in an *in vitro* chromosome aberration test conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with *cis*-4-(isopropyl)cyclohexanemethanol in DMSO at the following concentrations: 12.5, 25, 100, 150, and 200 μg/mL for the 4-h exposure in the presence and absence of S9 mix and 3.13, 6.25, 12.5, 25, 50, and

100 μg/mL for the 24-h exposure in the absence of S9 mix. No statistically significant increases in the frequency of cells with aberrations, in either of the 2 separate experiments, were observed (RIFM, 2012d). Under the conditions of the study, *cis*-4-(isopropyl)cyclohexanemethanol was considered unable to induce chromosome aberrations in the *in vitro* chromosome aberrations test.

Based on the available data, *cis*-4-(isopropyl)cyclohexanemethanol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/26/16.

10.1.2. Repeated Dose Toxicity

The MOE for *cis*-4-(isopropyl)cyclohexanemethanol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. The repeated dose toxicity data on *cis*-4-(isopropyl)cyclohexanemethanol are sufficient for the repeated dose toxicity endpoint. In a 14-day gavage GLP DRF study, groups of 5 male and 3 female rats/dose were gavaged daily with 0 (corn oil), 50, 150, 300, or 500 mg/kg/day of the test material *cis*-4-(isopropyl) cyclohexanemethanol. One week following the administration, since no observable adverse effects were reported, 2 additional groups were included at 750 and 1000 mg/kg/day. The 2 higher doses were not tolerated, and the animals were soon euthanized due to bodyweight loss and clinical signs (underactive or unresponsive behavior, abnormal gait, piloerection, partially closed eyes, and hunched posture). At 500 mg/kg/day, there was a reduction in bodyweight gains and an increase in liver weights among females. In addition to the systemic toxicity, the male reproductive system was adversely affected at doses of 300 and 500 mg/kg/day. Hence, a maximum dose of 300 mg/kg/day was selected for further follow-up studies (RIFM, 2013b). In an OECD 407 gavage 28-day study, groups of 5 rats/sex/dose were treated with the test material at doses of 0 (corn oil), 30, 100, or 300 mg/kg/day. In addition to effects on the male reproductive system, there was an increase in liver weights among high-dose males and all treated females. Periportal hepatocyte vacuolation was reported among high-dose males and all treated females. There was also an increase in aspartate aminotransferase levels among high-dose animals. The cholesterol levels were decreased among high-dose animals, and the bile acid and urea concentrations in the plasma were elevated among females at the highest dose. While these changes suggest possible alterations to intra-hepatocellular fat metabolism/transport in the high-dose animals, there was no evidence of degenerative liver changes in either sex at any dose levels. Hence, it was considered to be an adaptive response to treatment with the test material (RIFM, 2013c). Although there was an alteration in the plasma AST levels among the high-dose animals, this was not considered adverse in the absence of necrosis. Therefore, the NOAEL for repeated dose toxicity was determined to be 300 mg/kg/day, the highest dose tested. In another study, a GLP dietary 18-day repeated dose investigative study with a 4-week treatment-free recovery period was conducted on Crl:CD(SD) rats, with a focus on the male reproductive tract. Groups of 5 male and 3 female rats/dose were fed diets containing 0, 1500, 3000, 5000, or 7500 ppm (approximately 0, 109, 214, 353, or 493 mg/kg/day for males and 0, 142, 210, 339, or 499 mg/kg/day for females) of the test material for 18 days. Additional groups of 5 male rats/dose were fed diets containing 0, 5000, or 7500 ppm for 18 days, followed by a 4-week recovery period. In addition to the alteration in male reproductive parameters, at dose levels greater than 3000 ppm, reduced food consumption was observed in a dose-dependent manner, with a concomitant reduction in bodyweight gain. The bodyweight gain and food consumption values returned to normal during the recovery period. At 7500 ppm, a slightly increased relative liver weight was noted in both sexes. The liver weights returned to normal after the 4-week recovery period (RIFM, 2014a). This suggests that the liver weight and alteration in liver microscopy are reversible alterations to treatment with *cis*-4-(isopropyl) cyclohexanemethanol.

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 or 100 mg/kg/day.

Therefore, the *cis*-4-(isopropyl)cyclohexanemethanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-4-(isopropyl)cyclohexanemethanol NOAEL in mg/kg/day by the total systemic exposure to *cis*-4-(isopropyl)cyclohexanemethanol, 100/0.0091 or 10989.

In addition, the total systemic exposure to *cis*-4-(isopropyl)cyclohexanemethanol (9.1 μg/kg/day) is below the TTC (30 μg/kg/day) 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 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.

Additional References: RIFM, 2014b; RIFM, 2008b; RIFM, 2008a.

Literature Search and Risk Assessment Completed On: 02/15/17.

10.1.3. Developmental and Reproductive Toxicity

The MOE for *cis*-4-(isopropyl)cyclohexanemethanol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. The developmental toxicity data on *cis*-4-(isopropyl)cyclohexanemethanol are sufficient for the developmental toxicity endpoint. Groups of 10–12 rats/sex/dose were administered 0, 50, 150, or 300 mg/kg/day of the test material in corn oil daily via gavage. The study was conducted according to the OECD 421 reproduction/developmental toxicity screening test protocol. In one or more litters at 300 mg/kg/day, observations included total litter resorption *in utero*, short gestation length, reduced number of implantations, and small litter size. Litters were observed to have little or no milk in the stomach on day 1 post-partum, with several pups in each of these litters dying (reflected in a low pup viability index), and/or pups recorded as being cold to the touch. The live-birth index was unaffected by treatment at 300 mg/kg/day among litters with offspring surviving to day 7 of age, although the live-birth index was slightly lower than expected at 150 mg/kg/day (92.2%), reflecting an increased number of litters with losses of pups. The offspring viability index, bodyweights, and bodyweight gains were reduced at 300 mg/kg/day. The NOAEL for developmental toxicity was determined to be 50 mg/kg/day, since the pup live-birth index was slightly lower than the controls at 150 mg/kg/day, and there was one litter with several pup deaths where offspring bodyweights on day 1 of age were lower than expected at 300 mg/kg/day (RIFM, 2013d). Thus, the NOAEL for the developmental toxicity endpoint was determined to be 50 mg/kg/day. **Therefore, the *cis*-4-(isopropyl)cyclohexanemethanol MOE for the developmental toxicity endpoint can be calculated by dividing the *cis*-4-(isopropyl)cyclohexanemethanol NOAEL in mg/kg/day by the total systemic exposure to *cis*-4-(isopropyl) cyclohexanemethanol, 50/0.0091 or 5495.**

The reproductive toxicity data on *cis*-4-(isopropyl)cyclohexanemethanol are sufficient for the reproductive toxicity endpoint. A 14-day gavage GLP study was conducted on male rats with the test material to observe the effects on male reproductive organs after repeated oral administration. Groups of Crl:WI(Han) 5 male rats/group were treated with the test material at doses of 0 (olive oil), 50, and 1000 mg/kg/day for 14 days. Special attention was given to the reproductive organs. Epididymis-oligospermia and tubular degeneration of the

testicle were observed among all males of the high-dose group. No reproductive toxicity was reported among the males of the 50 mg/kg/day group (RIFM, 2010). Another 14-day gavage repeated DRF study was conducted on Crl:CD(SD) rats. Groups of 5 male and 3 female rats/dose were gavaged daily with 0 (corn oil), 50, 150, 300, or 500 mg/kg/day of the test material. Following the completion of one week of treatment, there was no clear evidence of adverse toxicity up to the highest dose of 500 mg/kg/day. Thus, additional groups of 3 male and 3 female rats/dose were gavaged with 750 or 1000 mg/kg/day for 7 days. Mortality was reported among the 2 high-dose groups. The male reproductive system was adversely affected, with a loss of sperm or reduction in sperm motility reported among the 300 and 500 mg/kg/day dose groups (RIFM, 2013b). Thus, the highest dose for further follow-up studies was set at 300 mg/kg/day. An OECD 407 gavage GLP study was conducted with *cis*-4-(isopropyl)cyclohexanemethanol on groups of 5 rats/sex/dose at dose levels of 0 (corn oil), 30, 100, or 300 mg/kg/day. In addition to the systemic toxicity parameters, the male reproductive system was also monitored. At 300 mg/kg/day, a reduction in sperm velocity with an increase in static sperm resulted in an overall reduction in the percentages of motile and progressively motile sperm. Thus, the NOAEL for reproductive toxicity was determined to be 100 mg/kg/day (RIFM, 2013c). In another study, groups of 10–12 rats/sex/dose were gavaged daily with 0, 50, 150, or 300 mg/kg/day *cis*-4-(isopropyl)cyclohexanemethanol in corn oil. The study was conducted according to the OECD 421 reproduction/developmental toxicity screening test protocol. At 300 mg/kg/day, treatment resulted in marked reductions in sperm motility, but no such effects were reported among the animals of the 150 and 50 mg/kg/day dose groups. There were no effects on estrous cycle measurements reported among the treated animals up to the highest dose tested (RIFM, 2013d). A GLP dietary 18-day repeated dose investigative study with a 4-week treatment-free recovery period was conducted on Crl:CD(SD) rats, with a focus on the male reproductive tract. Groups of 5 male and 3 female rats/dose were fed diets containing 0, 1500, 3000, 5000, or 7500 ppm (approximately 0, 109, 214, 353, or 493 mg/kg/day for males and 0, 142, 210, 339, or 499 mg/kg/day for females) of *cis*-4-(isopropyl)cyclohexanemethanol for 18 days. Additional groups of 5 male rats/dose were fed diets containing 0, 5000, or 7500 ppm for 18 days, followed by a 4-week recovery period. There was a reduction in the combined seminal vesicle/prostate/coagulating gland weights and epididymal weights among males. After the recovery period, the combined seminal vesicle/prostate/coagulating gland weights were still slightly reduced. An increase in the percentage of static sperm and a marked decrease in or absence of percentages of motile and/or progressively motile sperm attributable to the presence of decapitated sperm was reported among the high-dose group males. At 5000 ppm, one male showed low percentages of motile and progressively motile sperm, with a concomitant increase in the percentage of static sperm. There was also a suggestion of a general slight decrease in sperm velocity at this inclusion level. After the recovery period, sperm motility and motion parameters were slightly reduced at 7500 ppm, while the absolute values of most parameters were greatly improved compared to the end of the treatment period. It was concluded that the treatment-related effects observed on the sperm of male rats exposed by gavage administration could be slightly reduced by employing dietary administration (RIFM, 2014a). Thus, the NOAEL for the reproductive toxicity endpoint was determined to be 150 mg/kg/day, based on the OECD 421 study (RIFM, 2013d). **Therefore, the *cis*-4-(isopropyl)cyclohexanemethanol MOE for the reproductive toxicity endpoint can be calculated by dividing the *cis*-4-(isopropyl)cyclohexanemethanol NOAEL in mg/kg/day by the total systemic exposure to *cis*-4-(isopropyl)cyclohexanemethanol, 150/0.0091 or 16484.**

In addition, the total systemic exposure to *cis*-4-(isopropyl)cyclohexanemethanol (9.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1.1. Derivation of reference dose (RfD). Section IX provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008c; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.5 mg/kg/day.

The RfD for *cis*-4-(isopropyl)cyclohexanemethanol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.5 mg/kg/day.

Additional References: RIFM, 2008b; RIFM, 2008a; RIFM, 2013b; RIFM, 2014b.

Literature Search and Risk Assessment Completed On: 02/15/17.

10.1.4. Skin Sensitization

Based on the existing data, *cis*-4-(isopropyl)cyclohexanemethanol is considered to be an extremely weak skin sensitizer with a defined NESIL of 17000 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, *cis*-4-(isopropyl) cyclohexanemethanol is considered to be an extremely weak skin sensitizer with a defined NESIL of 17000 μg/cm^2. The chemical structure of *cis*-4-(Isopropyl)cyclohexanemethanol indicates that it is not predicted to be directly reactive to skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD Toolbox v3.4). In a murine local lymph node assay (LLNA), *cis*-4-(isopropyl)cyclohexanemethanol was found to be sensitizing with an EC3 value of 44% (11000 μg/cm^2) (RIFM, 2012c). In a confirmatory human repeated insult patch test (HRIPT) with 15% or 17717 μg/cm^2 of *cis*-4-(Isopropyl)cyclohexanemethanol in 1:3 diethyl phthalate:ethanol, no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2005). Based on the available data, *cis*-4-(isopropyl)cyclohexanemethanol is considered to be an extremely weak skin sensitizer with a defined NESIL of 17000 μg/cm^2 (Table 1). Section IX provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008c; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.5 mg/kg/day.

Table 1
Data Summary for *cis*-4-(isopropyl)cyclohexanemethanol.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
11000 [1]	Extremely weak	17717	NA	NA	17000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

Additional References: RIFM, 1975a; RIFM, 1975b; RIFM, 2000a; RIFM, 2000b.

Literature Search and Risk Assessment Completed On: 10/27/16.

10.1.5. Phototoxicity/photoallergenicity

Based on UV absorption spectra, *cis*-4-(isopropyl)cyclohexanemethanol 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 *cis*-4-(isopropyl)cyclohexanemethanol in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, *cis*-4-(isopropyl)cyclohexanemethanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no significant absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/06/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *cis*-4-(isopropyl)cyclohexanemethanol is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There is limited inhalation data available on *cis*-4-(isopropyl)cyclohexanemethanol. Based on the Creme RIFM Model, the inhalation exposure is 0.058 mg/day. This exposure is 24.1 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: UGCM, 1997.

Literature Search and Risk Assessment Completed On: 03/20/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *cis*-4-(isopropyl)cyclohexanemethanol 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, *cis*-4-(isopropyl)cyclohexanemethanol 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 v4.1 (US EPA, 2012a) identified *cis*-4-(isopropyl)cyclohexanemethanol as not 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 v4.1). 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 VoU (2015), *cis*-4-(isopropyl)cyclohexanemethanol presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2012g**:** The ready biodegradability of the test material was evaluated in a manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 74% was observed after 28 days.

10.2.3.2. Ecotoxicity. RIFM, 2012a**:** A 48-h *Daphnia magna* acute toxicity test was conducted according to the OECD 202 method. The EC50 for *cis*-4-(isopropyl)cyclohexanemethanol material to *Daphnia magna* based on nominal test concentrations was 13 mg/L.

RIFM, 2012e**:** A 96-h acute toxicity test was conducted with juvenile rainbow trout (*Oncorhynchus mykiss*) under semi-static test conditions following OECD 203 guidelines. The 96-h LC50 of *cis*-4-(isopropyl)cyclohexanemethanol based on nominal test concentrations was 4.2 mg/L.

RIFM, 2012f**:** A 72-h algae acute toxicity test was conducted according to OECD 201 guidelines. The EC50s based on the growth rate and yield were reported to be 10 mg/L and 6.0 mg/L, respectively.

10.2.4. Other available data

cis-4-(Isopropyl)cyclohexanemethanol has been pre-registered for REACH, but no additional data is available at this time.

10.2.5. Risk assessment refinement

Since *cis*-4-(Isopropyl) cyclohexanemethanol has passed the risk screening criteria, the measured ecotoxicity data is included for completeness only and is not used for PNEC calculation.

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)**	10.87			1000000	0.01087	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.339	4.117	5.334	10000	0.4117	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.48	3.48
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.4117 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, *cis*-4-(isopropyl)cyclohexanemethanol does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/15/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/23/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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