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Short Review

RIFM fragrance ingredient safety assessment, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol, CAS registry number 63500-71-0

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A B S T R A C T

2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol is not genotoxic, does not have skin sensitization potential, and provided an MOE > 100 for the repeated dose, developmental, and reproductive toxicity endpoints. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and data on 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol. The environmental endpoints were evaluated; 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol 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.

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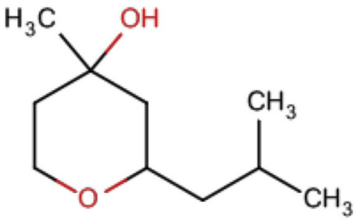
Version: 031918. This version replaces any previous versions.
Name: 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol
CAS Registry Number: 63500-71-0
Additional CAS Numbers*:65418-69-1 cis-Tetrahydro-2-isobutyl-4-methylpyran-4-ol (no use reported) 65418-70-4 trans-Tetrahydro-2-isobutyl-4-methylpyran-4-ol (no use reported)
*These materials are included in this assessment because the materials are isomers.



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., 2015, 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
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.
2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol is not genotoxic, does not have skin sensitization potential, and provided an MOE > 100 for the repeated dose, developmental, and reproductive toxicity endpoints. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and data on 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol. The environmental endpoints were evaluated; 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol 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, 2007; RIFM, 1994)
Repeated Dose Toxicity: NOAEL = 41.7 mg/kg/day.	(RIFM, 1989f)
Developmental and Reproductive Toxicity: NOAEL = 437.8 mg/kg/day.	(RIFM, 2015c; RIFM, 2015d)
Skin Sensitization: Not a concern for skin sensitization.	(RIFM, 2004b; RIFM, 2004a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB; RIFM, 1985b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 4.3% (OECD 301B)	RIFM (1997)
Bioaccumulation: Screening-level: 12.37 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint**:** 72-h algae EC50: > 94 mg/L	

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Environmental Safety Assessment
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 72-h algae EC50: > 94 mg/L RIFM (1996a)
RIFM PNEC is: 94 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

Chemical Name: 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol	Chemical Name: cis-Tetrahydro-2-isobutyl-4-methylpyran-4-ol	Chemical Name: trans-Tetrahydro-2-isobutyl-4-methylpyran-4-ol
CAS Registry Number: 63500-71-0	**CAS Registry Number:** 65418-69-1	**CAS Registry Number:** 65418-70-4
Synonyms: 2H-Pyran-4-ol, tetrahydro-4-methyl-2-(2-methylpropyl)-; Rozanol; Florol; Florosa; A mixture of cis-tetrahydro-2-isobutyl-4-methylpyran-4-ol and trans-tetrahydro-2-isobutyl-4-methylpyran-4-ol; Pyranol; (14)C-Pyranol; 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol	**Synonyms:** *cis*-Tetrahydro-2-isobutyl-4-methylpyran-4-ol	**Synonyms:** *trans*-Tetrahydro-2-isobutyl-4-methylpyran-4-ol
Molecular Formula: $C_{10}H_{20}O_2$	**Molecular Formula:** $C_{10}H_{20}O_2$	**Molecular Formula:** $C_{10}H_{20}O_2$
Molecular Weight: 172.68	**Molecular Weight:** 172.68	**Molecular Weight:** 172.68
RIFM Number: 5489	**RIFM Number:** 5489	**RIFM Number:** 5489
Stereochemistry: Isomer not specified. Two stereocenters and 4 total stereoisomers possible.	**Stereochemistry:** Cis isomer specified. Two stereocenters and 4 total stereoisomers possible.	**Stereochemistry:** Trans isomer specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

CAS # 63500-71-0	CAS # 65418-69-1	CAS # 65418-70-4
Boiling Point: 229.55 °C (EPI Suite)	Boiling Point: 229.55 °C (EPI Suite)	Boiling Point: N/A
Flash Point: > 200.00 °F; TCC (> 93.33 °C)*	**Flash Point:** 102 °C (GHS)	**Flash Point:** N/A
Log K_{OW}: 1.65 CV = 0.7% (RIFM, 1989a), 2.16 (EPI Suite)	**Log K_{OW}:** 1.65 CV = 0.7% (RIFM, 1989a), 2.16 (EPI Suite)	**Log K_{OW}:** N/A
Melting Point: 24.55 °C (EPI Suite)	**Melting Point:** 24.55 °C (EPI Suite)	**Melting Point:** N/A
Water Solubility: 28 g/L (RIFM, 1989a), 23.65 g/L at 23 °C (RIFM, 1989a), (calculated) 2773 mg/L (EPI Suite)	**Water Solubility:** 28 g/L (RIFM, 1989a), 23.65 g/L at 23 °C (RIFM, 1989a), (calculated) 2773 mg/L (EPI Suite)	**Water Solubility:** N/A
Specific Gravity: 0.94800 to 0.95500 @ 20.00 °C*	**Specific Gravity:** N/A	**Specific Gravity:** N/A
Vapor Pressure: 0.00712 mm Hg @ 20 °C (EPI Suite 4.0), 0.012 mm Hg @ 25 °C (EPI Suite)	**Vapor Pressure:** 0.00712 mm Hg @ 20 °C (EPI Suite 4.0), 0.012 mm Hg @ 25 °C (EPI Suite)	**Vapor Pressure:** N/A
UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})	**UV Spectra:**	**UV Spectra:**
Appearance/Organoleptic: Colorless to pale yellow clear oily liquid with a medium floral odor (fresh clean soft natural floral muguet linalool)	**Appearance/Organoleptic:** N/A	**Appearance/Organoleptic:** N/A

*as retrieved (08/28/13) from: http://www.thegoodscentscompany.com.

3. Exposure***

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 1.44% (RIFM, 2013b)
3. **Inhalation Exposure*:** 0.0019 mg/kg/day or 0.14 mg/day (RIFM, 2013b)
4. **Total Systemic Exposure**:** 0.015 mg/kg/day (RIFM, 2013b)

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

4. Derivation of systemic absorption

1. **Dermal:** 43.78%

RIFM, 2013a**:** An OECD/GLP 428 *in vitro* dermal penetration study was conducted using rat skin. The diffusion of ^{14}C-Pyranol into and through rat skin was assessed by single topical application of target concentrations of 9500 μg/cm^2 (950 mg/mL; pure) and 1000 μg/cm^2 (100 mg/mL; solution in corn oil) of test material to split thickness skin preparations under semi-occlusive conditions. During the study period, receptor fluids were collected from each cell at several time points (1, 2, 4, 6, 8, 10, and 24 h after application) in order to determine kinetic parameters (lag phase, absorption rate, and Kp). At the end of the sampling period, the test material was recovered from all compartments of each diffusion cell. The results of recovery are summarized as non-absorbed dose (donor chamber, skin washing, tape strips 1–2 and charcoal filter), amount associated with the skin preparation (skin and tape strips 3–6), and absorbed dose (receptor fluid, receptor chamber washing, receptor samples including wash out). The mean absorbed doses were 14.80% and 36.27% for skin treated with the high dose (950 mg/mL) and low dose (100 mg/mL), respectively. The amounts of test material associated with the skin after the exposure period amounted to 3.12% and 7.51% for the high dose and low dose, respectively. The sum of the absorbed dose and the amounts recovered in

skin preparation was calculated to determine the dermal absorption of pyranol, which corresponded to 17.92% and 43.78% of the applied dose for the high dose and low dose, respectively. The total recovery was 101.47% and 99.25% for the high and low dose, respectively. Thus, a dermal absorption value of 43.78% was used for this safety assessment.

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

Expert Judgment	ToxTree v2.6	OECD QSAR Toolbox v3.1
III	III	III

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

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

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

None of the materials included in this assessment are 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

Available; accessed on 03/19/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenicity of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was evaluated in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2 uvrA were treated with 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of S9. No significant increase in revertant colonies were observed in the strains at the concentrations tested (RIFM, 2007). Under the conditions of the study, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was negative in the Ames test.

The clastogenicity of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was assessed in an *in vitro* chromosome aberration study. Human peripheral blood lymphocytes were treated with 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol in ethanol at concentrations of to 2000, 3000, 4000, and 5000 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item without S9 metabolic activation. However, in the presence of S9 metabolic activation, small but reproducible statistically significant increases were observed in chromosomal aberrations at 4000 and 5000 μg/mL in the confirmatory assay (RIFM, 1993b). Under the conditions of the study, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was considered to be clastogenic to human cells. In order to verify the biological relevance of the results, the first study was followed up with an *in vivo* study. The clastogenic activity of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was assessed in an *in vivo* micronucleus study conducted in compliance with GLP regulations and in accordance with OECD 474. Groups of male and female NMRI mice were administered 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol in methylcellulose via oral gavage at the doses 150, 300, and 600 mg/kg body weight. After 24 h (lower and middle doses) or 48 h (top dose) animals were euthanized and samples prepared. No significant increase in the frequency of micronucleated polychromatic erythrocytes was observed in the animals at the concentrations tested (RIFM, 1994). Under the conditions of the study, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was considered negative in the *in vivo* micronucleus assay.

Based on the available data, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol does not present a concern for genotoxic potential.

Additional References: RIFM, 1985c; RIFM, 1988; RIFM, 1992b.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.1.2. Repeated dose toxicity

\The margin of exposure for 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol for the repeated dose toxicity endpoint. A GLP 4-week oral gavage toxicity study was conducted in Crl:CD(SD)BR strain rats. Groups of 10 rats/sex/dose were administered via gavage with test material 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol at doses of 0, 25, 125, or 625 mg/kg/day in 1% aqueous hydroxypropylmethylcellulose for 4 weeks. At 625 mg/kg/day, salivation after dosing and staining/wetting of fur was observed in both male and female animals. One high-dose female was found prostrate on day 25 of the study. Ketones were present in the urine of most high-dosed males, which was of significance since ketones were not normally found in the rat urine. The absolute and relative adrenal weights of high-dose females were also statistically significantly higher than the control group. Thus, the NOAEL for repeated dose toxicity was considered to be 125 mg/kg/day, based on clinical signs, increased urinary ketone levels (males only), and increased adrenal weights (females only) of animals in the high-dose group (RIFM, 1989f). In another study, an OECD/GLP 411 dermal 90-day toxicity study was conducted in Wistar rats. Groups of 10 rats/sex/dose were treated via dermal application with the test material at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil for 3 months (5 days per week). The

test material was applied to the clipped dorsal skin of the animals and covered for at least 6 h using a semi-occlusive dressing (4 layers of absorbent gauze and stretch bandage). There were no treatment-related adverse effects up to the highest dose tested. Thus, the NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2015a). An OECD/GLP 428 *in vitro* dermal penetration study conducted on rat skin determined a dermal absorption value of 43.78% (RIFM, 2013a; see Section IV). The most conservative NOAEL of 125 mg/kg/day was selected for this safety assessment.

A default safety factor of 3 was used when deriving a NOAEL from a 28-day 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 125/3 or 41.7 mg/kg/day.

Therefore, the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol NOAEL in mg/kg/day by the total systemic exposure to 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol, 41.7/0.015 or 2780.

*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: 08/08/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol for the developmental toxicity endpoint. An OECD/GLP 414 dermal prenatal developmental toxicity study was conducted in female Wistar rats. Groups of 25 pregnant female rats were treated with test material, pyranol at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil to the intact shaven dorsal skin using a semi-occlusive dressing (6 h/day) from gestation days (GD) 6 through 19. There were no treatment-related adverse effects observed on fetal morphology up to the highest dose tested, thus the NOAEL for developmental toxicity was considered to be 1000 mg/kg/day (RIFM, 2015d). In another study, an OECD/GLP 421 dermal reproductive/developmental toxicity screening test was conducted in Wistar rats. Groups of 10 rats/sex/dose were treated daily with test material at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil to the intact shaven dorsal skin using a semi-occlusive dressing (6 h/day). The animals were treated for 2-week premating, 3-week mating in both sexes, through gestation to approximately 2 weeks of the lactation period. There were no treatment-related adverse effects observed among the parental generation and F1 pups. Thus, the NOAEL for reproductive and developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2015c). To account for bioavailability following dermal application, data from a rat *in vitro* study (RIFM, 2013a; see Section IV) was used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 43.78% of the applied dose, the revised developmental toxicity NOAEL from the dermal study is 437.8 mg/kg/day.

Therefore, the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol NOAEL in mg/kg/day by the total systemic exposure to 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol, 437.8/0.015 or 29187.

There are sufficient reproductive toxicity data on 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol for the reproductive toxicity endpoint. An OECD/GLP 421 dermal reproductive/developmental toxicity screening test was conducted in Wistar rats. Groups of 10 rats/sex/dose were treated daily with test material pyranol at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil to the intact shaven dorsal skin using a semi-occlusive dressing (6 h/day). The animals were treated for 2-week premating, 3-week mating in both sexes, through gestation to approximately 2 weeks of the lactation period. There were no treatment-related adverse effects observed among the parental generation and F1 pups. Thus, the NOAEL for reproductive and developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2015c). A GLP 14-day oral gavage toxicity screening study was conducted in male Wistar rats. Groups of 5 male rats were administered via gavage with test material at doses of 0 or 1000 mg/kg/day in olive oil for 14 days. Sperm evaluation and gross and histopathology of male sexual organs did not reveal any treatment-related adverse effects at 1000 mg/kg/day, the only dose tested (RIFM, 2010). To account for bioavailability following dermal application, data from a rat *in vitro* study (RIFM, 2013a; see Section IV) was used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 43.78% of the applied dose, the revised reproductive toxicity NOAEL from the dermal study is 437.8 mg/kg/day.

Therefore, the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol NOAEL in mg/kg/day by the total systemic exposure to 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol, 437.8/0.015 or 29187.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/08/17.

10.1.4. Skin sensitization

Based on the existing data, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol 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 (Toxtree 2.6.13; OECD toolbox v3.4). 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA) (RIFM, 2016). In a murine local lymph node assay, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol was found to be negative up to the maximum tested concentration of 30% (RIFM, 2004a). In guinea pigs, two maximization tests did not present reactions indicative of sensitization (RIFM, 1989e; RIFM, 1992a). In a confirmatory human repeat insult patch test (HRIPT) with 4408 μg/cm2 of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol in 3:1 diethyl phthalate:ethanol, no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2004b). Additionally, another HRIPT with 8% 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol in white petrolatum had no reactions indicative of sensitization in any of the 57 volunteers (RIFM, 1985a). Based on weight of evidence from structural analysis and animal and human studies, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/08/17.

10.1.5. Phototoxicity/Photoallergenicity

Based on UV/Vis absorption spectra and existing data, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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, 2009). In a human

photoallergy study, topical application of an 8% solution of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol did not result in photoallergenicity (RIFM, 1985b). Based on lack of absorbance and human study data, 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/18/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.14 mg/day. This exposure is 3.4 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol 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, 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol 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 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol as possibly persistent but not 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, 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 current Volume of Use (IFRA, 2015), 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key Studies

10.2.3.1. Biodegradation. RIFM, 1989d**:** The biodegradation of the test material was determined according to OECD TG No. 301C. At 100 mg/L, average biodegrading was 7% by BOD, 4% by TOC, and 8% by GC.

RIFM, 1993a**:** The ready and ultimate biodegradability of the test material was determined by a sealed vessel test CO_2 production test according to the OECD 301B method. No signs of degradation were exhibited as the average extent of mineralization (after 28 days) was −0.1%.

RIFM, 1997**:** The inherent biodegradability of the test material was determined in a sealed vessel test CO_2 production test using an acclimatized inoculum from a modified semi-continuous activated sludge test (SCAS). The average extent of mineralization (after 28 days) in the sealed vessel test using an acclimatized inoculum was 4.3%.

10.2.3.2. Ecotoxicity. RIFM, 1989c**:** A 96-h fish (rainbow trout) acute study was conducted according to the OECD 203 method under static conditions. The LC50 of 354 mg/L was reported.

RIFM, 1996b**:** A *Daphnia magna* acute study according to the 92/69/EEC L383 method was conducted under static conditions. The calculated EC50 at 48 h was greater than 320 mg/L.

RIFM, 1989b**:** An acute *Daphnia magna* toxicity study was conducted under static conditions, and the 48-h EC50 was reported to be 803 mg/L.

RIFM, 2006**:** An algae growth inhibition test was conducted according to the OECD 201 method. No significant effect on inhibition of growth (biomass or growth rate) of algae was observed with the test material at a concentration of 100 mg/L for 72 h.

RIFM, 1996a**:** An algae growth inhibition test was conducted according to the OECD 201 method. There was no significant inhibition in rate of growth or biomass and the 72-h EC50s were greater than the highest geometric mean concentration tested, 94 mg/L.

RIFM, 2015b**:** An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 was reported to be 286 mg/L and > 1000 mg/L for yield and growth rate, respectively.

10.2.3.3. Other available data. 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol is registered under REACH with no additional data.

10.2.4. 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)**	469.61			1,000,000	0.4696	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	95.91	55.38	28.18	10,000	2.818	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	354					
Daphnia		320				
Algae		94		1000	94	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.65	1.65
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	> 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 94 µg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 08/3/17.

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.

Declaration of interests

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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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