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RIFM fragrance ingredient safety assessment, *p*-menthan-2-one, CAS Registry number 499-70-7

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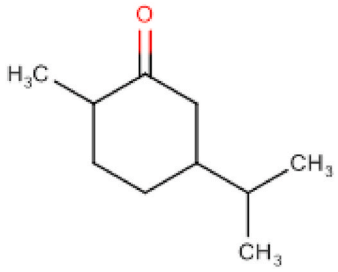

Name: *p*-Menthan-2-one CAS Registry Number: 499-70-7
Additional CAS Numbers*:
59471-80-6 Cyclohexanone, 2-methyl-5-(1-methylethyl)- (No Reported Use)
*Included because the materials are isomers

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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
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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
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.

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

p-Menthan-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-*tert*-butylcyclohexanone (CAS # 1728-46-7) show that *p*-menthan-2-one is not expected to be genotoxic. Data on read-across analog menthone (CAS # 10458-14-7) provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analog 2-sec-butylcyclohexanone (CAS # 14765-30-1) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from read-across analog menthone (CAS # 10458-14-7) provided *p*-menthan-2-one a NESIL of 10000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; *p*-menthan-2-one is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and the exposure to *p*-menthan-2-one is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; *p*-menthan-2-one 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 expected to be genotoxic.	(RIFM, 2017b; RIFM, 2017c)
Repeated Dose Toxicity: NOAEL = 6.67 mg/kg/day.	Madsen (1986)
Reproductive Toxicity: NOAEL = 226 mg/kg/day.	RIFM (2018)
Skin Sensitization: NESIL = 10000 μg/cm^2.	Rauen (2018)
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:	
Screening-level: 2.84 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 36.35 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 36.42 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 36.42 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.03642 μg/L	

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

Chemical Name: *p*-Menthan-2-one	Chemical Name: Cyclohexanone, 2-methyl-5-(1-methylethyl)-
CAS Registry Number: 499-70-7	**CAS Registry Number:** 59471-80-6
Synonyms: Carvomenthone; Cyclohexanone, 2-methyl-5-(1-	**Synonyms:** Cyclohexanone, 2-methyl-5-(1-methylethyl)-

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methylethyl)-, *trans*-; *trans*-5-Isopropyl-2-methylcyclohexan-1-one; Tetrahydrocarvone; 5-Isopropyl-2-methylcyclohexanone; *p*-Menthan-2-one	
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25	**Molecular Weight:** 154.25
RIFM Number: 6256	**RIFM Number:** 6256
Stereochemistry: *trans* isomer specified. Two stereocenters present and 2 stereoisomers possible.	**Stereochemistry:** Isomer not specified. Two stereocenters present and 2 stereoisomers possible.

2. Physical data*

1. **Boiling Point:** 212.98 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.87 (EPI Suite)
4. **Melting Point**: −1.82 °C (EPI Suite)
5. **Water Solubility:** 257.3 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.188 mm Hg at 20 °C (EPI Suite v4.0), 0.278 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

*Physical data is identical for both materials.

3. Volume of use (worldwide band)

1. <0.1 metric tons per year (IFRA, 2015)

4. Exposure*** to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.99% (RIFM, 2017a)
2. **Inhalation Exposure*:** 0.0000056 mg/kg/day or 0.00035 mg/day (RIFM, 2017a)
3. **Total Systemic Exposure**:** 0.0065 mg/kg/day (RIFM, 2017a)

*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 V. 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.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class II*, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	I

*See the Appendix below for further details.

6.2. Analogs Selected

a. **Genotoxicity:** 2-*tert*-Butylcyclohexanone (CAS # 1728-46-7)
b. **Repeated Dose Toxicity:** Menthone (CAS # 10458-14-7)
c. **Reproductive Toxicity:** 2-sec-Butylcyclohexanone (CAS # 14765-30-1)
d. **Skin Sensitization:** Menthone (CAS # 10458-14-7)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

p-Menthan-2-one is reported to occur in the following foods by the VCF*:

Citrus fruits
Mentha oils
Starfruit (*Averrhoa carambola* L.)

Cyclohexanone, 2-methyl-5-(1-methylethyl)- is not reported to occur in foods 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.

9. REACH dossier

p-Menthan-2-one is pre-registered for 2010. Cyclohexanone, 2-methyl-5-(1-methylethyl)- is pre-registered for 2018. No dossier is available for either material as of 03/11/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-menthan-2-one are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.0019
2	Products applied to the axillae	0.0019
3	Products applied to the face/body using fingertips	0.0019
4	Products related to fine fragrances	1.9
5A		0.079

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0019
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.019
5D	Baby cream, oil, talc	0.00064
6	Products with oral and lip exposure	0.027
7	Products applied to the hair with some hand contact	0.0019
8	Products with significant ano-genital exposure (tampon)	0.00064
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.054
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.0019
10B	Aerosol air freshener	0.0019
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.00064
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.0019

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 *p*-menthan-2-one, the basis was the reference dose of 0.067 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 10000 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *p*-menthan-2-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of *p*-menthan-2-one; however, read-across can be made to 2-*tert*-butylcyclohexanone (CAS # 1728-46-7; see Section VI).

The mutagenic activity of 2-*tert*-butylcyclohexanone 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 2-*tert*-butylcyclohexanone in 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, 2-*tert*-butylcyclohexanone was not mutagenic in the Ames test, and this can be extended to *p*-menthan-2-one.

The clastogenic activity of 2-*tert*-butylcyclohexanone 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 2-*tert*-butylcyclohexanone in DMSO at concentrations up to 1543 μg/mL in the dose range finding (DRF) study. Micronuclei analysis was conducted at concentrations up to 249 μg/mL in the presence and absence of S9 for 3 h and in the absence of metabolic activation for 24 h 2-*tert*-Butylcyclohexanone did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017c). Under the conditions of the study, 2-*tert*-butylcyclohexanone was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to *p*-menthan-2-one.

Based on the available data, *p*-*tert*-butylcyclohexanone does not present a concern for genotoxic potential, and this can be extended to *p*-menthan-2-one.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/17/20.

11.1.2. Repeated dose toxicity

The MOE for *p*-menthan-2-one is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no data on the target material to support the repeated dose toxicity endpoint. Read-across material menthone (CAS # 10458-14-7; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a gavage subchronic toxicity study, 10 Wistar rats/sex/dose were administered menthone (purity: 97%) at doses of 0, 200, 400, and 800 mg/kg/day for 28 days. However, severe weakening was observed along with pale mucous membranes and signs of pain in females receiving the highest dose. Thus, the maximum dose for females was adjusted to 400 mg/kg/day after study day 19, and therefore, the highest average dose for females was 671 mg/kg/day. A significant decrease in food consumption, body weight, and bodyweight gain was observed during the study. However, in males, these effects were observed only at the highest dose. Furthermore, a dose-dependent decrease in creatinine and a dose-dependent increase in ALP and bilirubin were observed in both sexes. Due to the decreased body weights in both sexes, relative organ weights of the brain, spleen, liver, and kidneys were increased significantly. Microscopic evaluation of the brain revealed cyst-like spaces in the cerebellum in animals of both sexes at mid- and high-doses. Since treatment-related effects were observed at the lowest dose, an accurate NOAEL could not be determined for this study. Hence, **200 mg/kg/day was considered to be the LOAEL for the repeated dose toxicity endpoint** (Madsen, 1986).

A default safety factor of 10 was used when deriving a NOAEL from a LOAEL (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 200/10 or 20 mg/kg/day.

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety *. **Thus, the derived NOAEL for the repeated dose toxicity endpoint is 20/3 or 6.67 mg/kg/day**.

Therefore, the *p*-menthan-2-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the menthone NOAEL in mg/kg/day by the total systemic exposure to *p*-menthan-2-one, 6.67/0.0065 or 1026.

In addition, the total systemic exposure to *p*-menthan-2-one (6.5 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Section X 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, 2020) and a reference dose of 0.067 mg/kg/day.

Derivation of reference dose (RfD). The RIFM Criteria Document (Api,

2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for *p*-menthan-2-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 6.67 mg/kg/day by the uncertainty factor, 100 = 0.067 mg/kg/day.

*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: 12/15/20.

11.1.3. Reproductive toxicity

The MOE for *p*-menthan-2-one is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on *p*-menthan-2-one. Read-across material 2-sec-butylcyclohexanone (CAS # 14765-30-1; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Wistar Hans rats/sex/dose were fed diets containing 2-sec-butylcyclohexanone at doses of 0 (basal diet only), 650, 2000, or 6000 ppm (mean daily intake of 0, 48, 151, and 377 mg/kg/day for males and 0, 88, 226, and 508 mg/kg/day for females, respectively). The animals were dosed for 2 weeks prior to mating, during mating, and continued until euthanasia for males (at least 28 days) and up to 13 days after delivery for females (51–56 days for females with offspring and 42 days for females without offspring). In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. High-dose dams exhibited statistically significant decreases in body weight and bodyweight gain, which was associated with decreased food consumption throughout the pre-mating, post-coitum, and lactation periods. Four females were not pregnant despite evidence of mating (1 control, 2 low-dose, and 1 high-dose), in which no abnormalities were observed in the reproductive organs. At 6000 ppm, significant changes in the length of estrous cycles (1/10 dams) and acyclic estrous cycles (6/10 dams) were reported. However, most of these dams had normal litters, and no abnormalities were observed in the reproductive organs that could account for the effect on estrous cyclicity. This effect was considered to be possibly a secondary effect of the bodyweight loss (and stress related to the severely-reduced food consumption) in the first treatment week (when vaginal lavage samples for estrous cycle examination were collected). One mid-dose dam (with a normal litter) also exhibited an acyclic estrous cycle, which can sporadically occur as a background finding (1/316 control females, period 2015–2017). Given the low incidence of this finding (1/10 females), and in the absence of other potentially treatment-related reproductive or developmental effects at this dose, this incidence was not considered to be adverse. Statistically significant decreases in pup body weight and bodyweight gain were reported at 6000 ppm from birth (10%) and on PND 13 (30%). No other treatment-related adverse effects were reported for fertility or on the development of pups. Thus, the NOAEL for effects on fertility was considered to be 2000 ppm or 226 mg/kg/day, based on alterations in the length of estrous cycles and acyclic estrous cycles observed among the high-dose group dams. The NOAEL for developmental toxicity was considered to be 2000 ppm or 226 mg/kg/day, based on decreased pup body weight among high-dose group pups (RIFM, 2018; also available at ECHA, 2018). **Therefore, the *p*-menthan-2-one MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-sec-butylcyclohexanone NOAEL in mg/kg/day by the total systemic exposure to *p*-menthan-2-one, 226/0.0065 or 34769.**

In addition, the total systemic exposure to *p*-menthan-2-one (6.5 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/15/20.

11.1.4. Skin sensitization

Based on the existing data and read-across material menthone (CAS # 10458-14-7), *p*-menthan-2-one is considered a skin sensitizer with a defined NESIL of 10000 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for *p*-menthan-2-one. Based on the existing data and read-across material menthone (CAS # 10458-14-7; see Section VI), *p*-menthan-2-one is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). No *in chemico* or *in vitro* studies are available for this material or the read-across material. In a murine local lymph node assay (LLNA), a mixture containing read-across materials *trans*-p-menthan-3-one (23.5%) and *d,l*-isomenthone (76.1%) was found to be sensitizing with an EC3 value of 40.6% (10150 μg/cm^2; RIFM, 2012). In another murine LLNA, another mixture containing 2 other read-across materials, *l*-menthone (84.5%) and *d*-isomenthone (15.1%) was found to be sensitizing with an EC3 value of 54.2% (13550 μg/cm^2, RIFM, 2012). In a human maximization test, no skin sensitization reactions were observed with the read-across materials menthone and *d,l*-isomenthone (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 10038 μg/cm^2 of a mixture containing read-across materials menthone (77.5%) and *d,l*-isomenthone (22.2%) in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 107 volunteers (Rauen, 2018).

Based on the available data on read-across material menthone, summarized in Table 1, *p*-menthan-2-one is considered to be a weak skin sensitizer with a defined NESIL of 10000 μg/cm^2. Section X 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, 2020) and a reference dose of 0.067 mg/kg/day.

Additional References: RIFM, 1962.

Literature Search and Risk Assessment Completed On: 12/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *p*-menthan-2-one would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Data Summary for menthone as read-across for *p*-menthan-2-one.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
11850 [2]	Weak	10038	5520	N/A	10000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; N/A = Not Available.

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *p*-menthan-2-one 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, 2009). Based on the lack of absorbance, *p*-menthan-2-one does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. 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: 12/11/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *p*-menthan-2-one is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on *p*-menthan-2-one. Based on the Creme RIFM Model, the inhalation exposure is 0.00035 mg/day. This exposure is 1343 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: UGCM, 1997; Perrucci (1995); Rice (1994).

Literature Search and Risk Assessment Completed On: 12/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-menthan-2-one was performed following the RIFM Environmental Framework (Salvito, 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, *p*-menthan-2-one 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 *p*-menthan-2-one 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, 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *p*-menthan-2-one presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

Biodegradation. No data available.

Ecotoxicity. No data available.

Other available data. p-Menthan-2-one has been pre-registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.87	2.87
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use.

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

The RIFM PNEC is 0.03642 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/16/20.

12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	36.42			1000000	0.03642	

&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/

12.1. 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 03/11/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112496.

Appendix

Read-across Justification

Methods

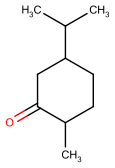
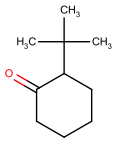
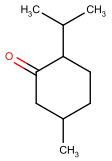
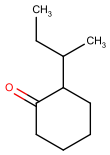
The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- 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 material 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	*p*-Menthan-2-one	2-*tert*-Butylcyclohexanone	Menthone	2-sec-Butylcyclohexanone
CAS No.	499-70-7	1728-46-7	10458-14-7	14765-30-1
Structure				

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
				
Similarity (Tanimoto Score)		0.94	0.97	0.94
Read-across Endpoint		• Genotoxicity	• Repeated Dose Toxicity • Skin Sensitization	• Reproductive Toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$	$C_{10}H_{18}O$	$C_{10}H_{18}O$
Molecular Weight	154.25	154.25	154.25	154.25
Melting Point (°C, EPI Suite)	−1.82	8.41	−6.00	1.92
Boiling Point (°C, EPI Suite)	212.98	210.92	207.00	218.54
Vapor Pressure (Pa @ 25°C, EPI Suite)	37.06	40.93	49.33	28.26
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.87	2.91	3.05	2.94
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.57E+02	2.40E+02	4.97E+02	2.23E+02
J_{max} (μg/cm^2/h, SAM)	17.47	17.06	41.27	16.40
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.61E+01	1.61E+01	1.61E+01	1.61E+01
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found		
Carcinogenicity (ISS)	• No alert found	• No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group			• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)			• Toxicant (good reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found		• No alert found	
Protein Binding (OECD)	• No alert found		• No alert found	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)		• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No skin sensitization reactivity domain alerts identified		• No skin sensitization reactivity domain alerts identified	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• See Supplemental Data 4

Summary

There are insufficient toxicity data on *p*-menthan-2-one (CAS # 499-70-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2-*tert*-butylcyclohexanone (CAS # 1728-46-7), menthone (CAS # 10458-14-7), and 2-sec-butylcyclohexanone (CAS # 14765-30-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-*tert*-Butylcyclohexanone (CAS # 1728-46-7) was used as a read-across analog for the target material *p*-menthan-2-one (CAS # 499-70-7) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of cyclohexanones.
  - o The target material and the read-across analog share a cyclohexanone ring. Both molecules are structural isomers.
  - o The key difference between the target material and the read-across analog is that the target material has an isopropyl branch in position 3 and a methyl substituent in position 6, whereas the read-across analog has a *tert*-butyl branch in position 2. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- There are no toxicological alerts for the target material as well as for the read-across analog. Data are consistent with *in silico* alerts.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Menthone (CAS # 10458-14-7) was used as a read-across analog for the target material *p*-menthan-2-one (CAS # 499-70-7) for the skin sensitization and repeated dose toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of cyclohexanones.
  - The target material and the read-across analog share a cyclohexanone ring and isopropyl and methyl substituents. Both molecules are structural isomers.
  - The key difference between the target material and the read-across analog is the position of the isopropyl and methyl branches, which are respectively in positions 3 and 6 for the target material and positions 2 and 5 for the read-across analog. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have a toxicant alert for developmental toxicity (CAESAR v2.1.6). The data described in the reproductive toxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by the data.
  - There are no toxicological alerts for the target material as well as for the read-across analog. Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-sec-Butylcyclohexanone (CAS # 14765-30-1) was used as a read-across analog for the target material *p*-menthan-2-one (CAS # 499-70-7) for the reproductive toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of cyclohexanones.
  - The target material and the read-across analog share a cyclohexanone ring. Both molecules are structural isomers.
  - The key difference between the target material and the read-across analog is that the target material has an isopropyl branch in position 3 and a methyl substituent in position 6, whereas the read-across analog has a *sec*-butyl branch in position 2. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have a toxicant alert for developmental toxicity (CAESAR v2.1.6). The data described in the reproductive toxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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 between 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.

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, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Intermediate (Class II)

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