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Short review

RIFM fragrance ingredient safety assessment, Isopulegol, CAS Registry Number 89-79-2

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ABSTRACT

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

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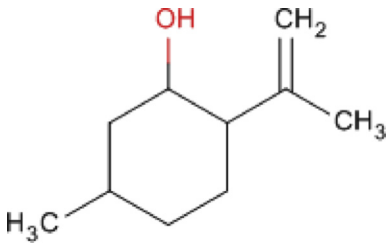
CAS Registry Number: 89-79-2



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015; #68218) which should be referred to for clarifications.

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

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

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity Not genotoxic (RIFM, 1993; RIFM, 2015; ECHA REACH Dossier)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not sensitizing (Klecak, 1985; RIFM, 1971; RIFM, 1994)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV spectra, RIFM DB; RIFM, 1994)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 73% (OECD 301D) (RIFM, 2000)
Bioaccumulation: Screening Level: 78.25 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* LC50: 4.76 mg/l (EpiSuite ver 4.1)

(*continued*)

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: 48 h *Daphnia magna* LC50: 4.76 mg/l (EpiSuite ver 4.1)
RIFM PNEC is: 0.476 μg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name**: Isopulegol
2. **CAS Registry Number**: 89-79-2
3. **Synonyms:** Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, [1R-(1.α.,2.β.,5.α.)]-, Isopulegol, p-8(9)-Menthen-3-ol, 1-Methyl-4-isopropenylcyclohexan-3-ol, Coolact P, 5-Methyl-2-(1-methylvinyl)cyclohexan-1-ol, Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, *p*-Menth-8-en-3-ol, メチルイソプロペニルシクロヘキサノール, 2-Isopropenyl-5-methylcyclohexanol
4. **Molecular Formula**: $C_{10}H_{18}O$
5. **Molecular Weight**: 154.25
6. **RIFM Number**: 218

2. Physical data

1. **Boiling Point:** 218 °C [FMA database], (calculated) 223.77 °C [EPI Suite]
2. **Flash Point:** 175 °F; CC [FMA database]
3. **Log K_{OW}**: 3.37 [EPI Suite]
4. **Melting Point**: −4.85 °C [EPI Suite]
5. **Water Solubility:** 308.6 mg/L [EPI Suite]
6. **Specific Gravity**: 0.909 [FMA database]
7. **Vapor Pressure:** 0.00263 mm Hg @ 20 °C [EPI Suite 4.0], 0.02 mm Hg 20 °C [FMA database], 0.00496 mm Hg @ 25 °C [EPI Suite]
8. **UV spectra:** No absorbance in the region of 290–700 nm; molar absorption is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with minty-herbaceous, bitter-sweet odor.

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year [IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics**: 0.06% [IFRA, 2011]
3. **97.5**th **Percentile:** 0.027% [IFRA, 2006]
4. **Dermal Exposure*:** 0.0007 mg/kg/day [IFRA, 2006]
5. **Oral Exposure**: Not available
6. **Inhalation Exposures**:** 0.000042 mg/kg/day or 0.0025 mg/day [IFRA, 2006]
7. **Total Systemic Exposure (Dermal + Inhalation)**: 0.00074 mg/kg/day

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby, 2002; Ford, 2000).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available — not considered.
3. **Inhalation**: Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.00074 mg/kg/day

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. Analogues 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 considered 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)

Isopulegol is reported to occur in the following foods* and in some natural complex substances (NCS):

Black currants (Ribes nigrum L.)
Buchu oil
Calabash nutmeg (Monodora myristica Dunal)
Citrus fruits
Ginger (Zingiber species)

Grape brandy
Lemon balm (Melissa officinalis L.)
Mastic (Pistacia lentiscus)
Mentha oils
Passion fruit (Passiflora species)
Xylopia species

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

8. IFRA standard

None.

9. REACH Dossier

Available; accessed on 10/14/2013.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, isopulegol does not present a concern for genotoxic potential.

10.1.2. Risk assessment

Isopulegol was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2016). The mutagenic potential of isopulegol was assessed in a GLP compliant bacterial reverse mutation test performed in accordance with OECD TG 471 using the modified, preincubation method. *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP2uvrA were treated with isopulegol in DMSO (dimethyl sulfoxide) at six dose levels, in duplicate, both with and without the addition of a rat liver homogenate metabolizing system (S9) (RIFM, 1993). No significant increase in the numbers of revertant colonies was recorded for any of the bacterial strains at any dose of isopulegol, with or without metabolic activation. These results were confirmed in a GLP OECD 471 study in 2010 (ECHA REACH Dossier: isopulegol). Isopulegol was found to be non-mutagenic under the conditions of this test.

The clastogenic activity of isopulegol was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with isopulegol in DSMO at concentrations ranging 0–1540 μg/plate in the presence and absence of metabolic activation for up to 24 h. The percentage of cells with micronucleated binucleated cells in the test substance-treated groups was not statistically significantly increased relative to vehicle control at any dose level (RIFM, 2015). Under the conditions of the study, isopulegol was considered not clastogenic in the *in vitro* micronucleus assay.

Based on the available data, isopulegol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/22/13.

10.1.3. Repeated dose toxicity

There are insufficient repeated dose data on isopulegol or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.4. Risk assessment

The repeated dose data on isopulegol are insufficient for the repeated dose toxicity endpoint. There are no repeated dose data on any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.74 μg/kg bw/day) is below the TTC for isopulegol (30 μg/kg bw/day).

Additional References: Bhatia, 2008a; Belsito, 2008; JECFA, 2001; Imaizumi, 1985; Boutin, 1985; RIFM, 1999; Bhatia, 2008b; JECFA, 2000; Stoner, 1973; Bhatia, 2008c; Bhatia, 2008d; Shimada, 2002; Jager, 2000; Crowell, 1992; JECDB: 4-(1-Methylethenyl) phenol.

Literature Search and Risk Assessment Completed on: 11/22/13.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental or reproductive data on isopulegol or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.6. Risk assessment

There are no developmental or reproductive data on isopulegol or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure (0.74 μg/kg bw/day) is below the TTC for isopulegol (30 μg/kg bw/day).

Additional References: Bhatia, 2008a; Belsito, 2008; JECFA, 2001; Imaizumi, 1985; Boutin, 1985; RIFM, 1999; Bhatia, 2008b; JECFA, 2000; Stoner, 1973; Bhatia, 2008c; Bhatia, 2008d; Shimada, 2002; Jager, 2000; Crowell, 1992; JECDB: 4-(1-Methylethenyl) phenol.

Literature Search and Risk Assessment Completed on: 11/22/13.

10.1.7. Skin sensitization

Based on the existing data, isopulegol does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data, isopulegol does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts, 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig test methods no reactions indicative of sensitization were observed (Klecak, 1985; RIFM, 1994). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test (RIFM, 1971).

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/22/13.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and existing data, isopulegol does not present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

UV/Vis absorption spectra for isopulegol indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry,

2009). In a Guinea pig phototoxicity study no reactions indicative of phototoxic responses were observed following application of up to 50% isopulegol (RIFM, 1994). Based on lack of absorbance and existing *in vivo* study data, isopulegol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/01/16.

10.1.10.1. Local respiratory toxicity. The margin of exposure could not be calculated due to lack of appropriate data. The material, Isopulegol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.11. Risk assessment

There are no inhalation data available on Isopulegol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.027%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.0025 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 560 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 5/26/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of isopulegol was performed following the RIFM Environmental Framework (Salvito, 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, isopulegol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify isopulegol as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), isopulegol does present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 2000a**: Biodegradation of the test material was evaluated in a closed bottle test according to the OECD 301D method. Under conditions of the study, 2.4 mg/l of isopulegol reached a biodegradation of 73% after 28 days.

10.2.3.2. Ecotoxicity. **RIFM, 2000b**: A 48 h *Daphnia magna* acute toxicity test was conducted according to the OECD 202 method. Under the conditions of the study, the 48-h EC50 was 45.5 mg/l.

10.2.4. Other available data

Isopulegol is registered under REACH and the following additional data is available (accessed 11/25/13):

A 48 h acute *Daphnia Magna* study has been conducted, and the EC50 of 533.2 mg/l was reported.

10.2.5. Risk assessment refinement

Since Isopulegol has passed the screening criteria, measured data is included for completeness only and has not been used for PNEC calculations.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	13.37 mg/l			1,000,000	0.0133 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	7.386 mg/l	4.761 mg/l	5.994 mg/l	10,000	0.476 μg/l	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.37	3.37
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.476 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/22/13.

11. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.08.001.

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