Food and Chemical Toxicology 134 (2019) 110726

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, isobornyl methyl ether, CAS Registry Number 5331-32-8

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ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/Photoallergenicity
Local respiratory toxicity
Environmental safety

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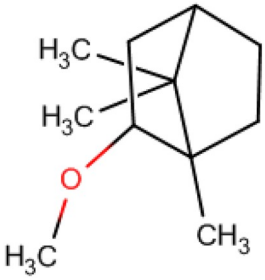
https://doi.org/10.1016/j.fct.2019.110726
Received 20 December 2018; Received in revised form 16 May 2019; Accepted 26 July 2019
Available online 29 July 2019

Version: 121818. This version replaces any previous versions.
Name: Isobornyl methyl ether
CAS Registry Number: 5331-32-8



Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
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
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.
Isobornyl methyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data and data from the read-across analog, 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane (CAS # 31996-78-8), show that isobornyl methyl ether is not expected to be genotoxic. Based on existing data and the application of the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2, isobornyl methyl ether does not present a safety concern for skin sensitization under the current, declared levels of use. Data from read-across analogs, 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane (CAS # 31996-78-8) and isobornyl acetate (CAS # 125-12-2), provide an MOE $>$ 100 for the repeated dose and reproductive toxicity endpoints, respectively. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class III material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; isobornyl methyl ether is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; isobornyl methyl ether was found not to be PBT as per 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, 2016b; RIFM, 2017b)
Repeated Dose Toxicity: NOAEL = 18.3 mg/kg/day. (ECHA Dossier: Reaction Mass of 5-ethylbicyclo[2.2.1]hept-2-yl methyl ether and 6-ethylbicyclo[2.2.1]hept-2-yl methyl ether and 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane; ECHA, 2012a)
Reproductive Toxicity: Developmental Toxicity: NOAEL = 1000 mg/kg/day. Fertility: NOAEL = 300 mg/kg/day. (ECHA Dossier: Exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acetate; ECHA, 2012b; RIFM, 2017a)
Skin Sensitization: No safety concerns at current, declared use levels. Exposure is below the DST.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening-level: 2.39 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 102 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-hour *Daphnia magna* LC50: 3.66 - mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-hour *Daphnia magna* LC50: 3.66 - mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.366 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

1. Identification

1. **Chemical Name:** Isobornyl methyl ether
2. **CAS Registry Number:** 5331-32-8
3. **Synonyms:** Bicyclo[2.2.1]heptane, 2-methoxy-1,7,7-trimethyl-, exo-; exo-2-Methoxy-1,7,7-trimethylnorbornane; exo-2-Methoxybornane; exo-2-Methoxy-1,7,7-trimethylbicyclo(2.2.1)heptane; 2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane; Isobornyl methyl ether
4. **Molecular Formula:** $C_{11}H_{20}O$
5. **Molecular Weight:** 168.28
6. **RIFM Number:** 94
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 8 stereoisomers possible

2. Physical data

1. **Boiling Point:** 182.22 °C (US EPA, 2012a)
2. **Flash Point:** 52 °C (GHS), 52 °C (RIFM Database)
3. **Log K_{OW}:** 3.55 (US EPA, 2012a)
4. **Melting Point:** 13.61 °C (US EPA, 2012a)
5. **Water Solubility:** 58.15 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.919–0.923 @ 20 °C (RIFM Database)
7. **Vapor Pressure:** 0.841 mm Hg @ 20 °C (US EPA, 2012a), 1.19 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} . cm^{-1})
9. **Appearance/Organoleptic:** A colorless to pale yellow liquid with a fresh, herbaceous, rosemary odor

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0062% (RIFM, 2016a)
3. **Inhalation Exposure*:** 0.000025 mg/kg/day or 0.0017 mg/day (RIFM, 2016a)
4. **Total Systemic Exposure**:** 0.00023 mg/kg/day (RIFM, 2016a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

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

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

2. Analogs Selected:
   a. **Genotoxicity:** 1-Ethyl-3-methoxytricyclo[2.2.1.02,6]heptane (CAS # 31996-78-8)
   b. **Repeated Dose Toxicity:** 1-Ethyl-3-methoxytricyclo[2.2.1.02,6]heptane (CAS # 31996-78-8)
   c. **Reproductive Toxicity:** Isobornyl acetate (CAS # 125-12-2)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Isobornyl methyl ether is reported to occur in the following food by the VCF* and is not found in natural complex substances (NCS):

7.1. Citrus fruits

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 12/18/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, isobornyl methyl ether does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Isobornyl methyl ether was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2014). The mutagenic activity of isobornyl methyl ether 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 isobornyl methyl ether in ethanol 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, 2016b). Under the conditions of the study, isobornyl methyl ether was not mutagenic in the Ames test.

The clastogenic activity of isobornyl methyl ether 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 isobornyl methyl ether in ethanol at concentrations up to 1680 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Isobornyl methyl ether did not induce binucleated cells with micronuclei when tested up to cytotoxic concentration levels in the absence of an S9 activation system. However, a statistically significant and dose-dependent increase in micronuclei induction was observed in the presence of metabolic activation for the 4-hour treatment period. Although the induced values were within the historical control range (0.0%–1.5%), they fell outside of the 95% control limit of historical control data (upper limit of 95% control limit = 0.0%–0.78%). These results were also reproduced in a repeat assay, but the Conchron-Armitage test was negative for dose-response in the repeat study; hence, the final result was considered to be equivocal (RIFM, 2017b). Under the conditions of the study, isobornyl methyl ether was considered to be producing an equivocal response in presence of metabolic activation.

Due to the equivocal response observed in the *in vitro* micronucleus study, a follow up 3D skin micronucleus assay was conducted. A GLP-compliant 3D reconstructed skin micronucleus (RSMN) assay was conducted to evaluate the genotoxic potential of isobornyl methyl ether in EpiDerm. Acetone was used as the vehicle. EpiDerm tissues were treated with isobornyl methyl ether at 24-hour intervals for 48 and 72 h at concentrations up to 70 mg/mL. Isobornyl methyl ether did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations, and therefore, it was concluded to be negative for the induction of micronuclei in the RSMN assay in EpiDerm (Roy, 2017a).

Additionally, results from an *in vivo* micronucleus study conducted on read-across material 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane (CAS # 31996-78-8) were negative. The clastogenic activity of 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and equivalent with OECD TG 474. The test material was administered in propylene glycol via intra gastric gavage to groups of male and female CD-1 mice. A single dose of 3519 mg/kg body weight was administered, and the mice were euthanized at 24, 48, or 72 h. The bone marrow was then extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1988). Under the conditions of the study, 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to isobornyl methyl ether.

Based on the data available, isobornyl methyl ether does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/27/17.

10.1.2. Repeated dose toxicity

The margin of exposure for isobornyl methyl ether is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on isobornyl methyl ether. Read-across material 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane (CAS # 31996-78-8; see Section 5) has sufficient repeated dose toxicity data. An OECD 407/GLP oral gavage repeated dose toxicity study was conducted in Crl:CD Sprague Dawley (BR strain) rats. Groups of 5 rats/sex/dose were administered daily with 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane at doses of 0, 5, 55, or 800 mg/kg/day for 28 days. No recovery group was used in the study. No mortalities were reported. At 800 mg/kg/day, increased salivation and hunched posture were reported for all rats, which persisted for 1 to several days. No treatment-related adverse effects were reported for body weight and food consumption. In high-dose group animals, a statistically significant (in most instances) increase in lymphocyte counts (resulting in higher total white blood cell [WBC] counts) was reported. In treated females, thrombotest times were significantly lower ($p < 0.05$ or $p < 0.01$) when compared to the controls. However, the magnitude of lower female thrombotest times was very low, and a similar effect was not observed among treated male rats. Therefore, it was considered not to be of toxicological importance. In clinical chemistry, statistically significant changes were reported in plasma for urea nitrogen (increase, males: high dose), cholesterol (increase, females: high dose), calcium (increase, males: high dose; females: mid and high dose), potassium (increase, males: high dose), inorganic phosphorus (increase, females), and chloride (decrease, males: high dose) levels. In the high-dose group, statistically significant increases in the adjusted liver weights (both sexes) and adrenal weights (males) were reported when compared to the controls. Histopathological changes were reported for the kidney (eosinophilic inclusions in the cortical tubular epithelium, males of all treatment groups) and liver (cytoplasmic rarefaction of periportal hepatocytes, 4 males and 2 females of the high-dose group). Renal pelvic dilatation was reported among the control (1 female rat), low-dose (1 female rat), mid-dose (1 male and 1 female rat), and high-dose (3 females) animals. It was reported that renal pelvic dilatation was common among rats of this strain, but the significance of the increase in incidence and degree of this finding in female rats treated at 800 mg/kg/day was not clear when compared with the control group. Dilatation of the ureters was also reported in 2/3 female rats that showed renal pelvic dilatation in

the high-dose group. Effects observed in the kidney among treated male rats were consistent with a condition known as hydrocarbon nephropathy, which occurs only in male rats and is not considered hazardous to human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). The NOAEL was considered to be 55 mg/kg/day, based on alterations in hematology (lymphocytes), clinical chemistry (urea nitrogen, cholesterol, calcium, potassium, inorganic phosphorous, and chloride), organ weights (liver and adrenal) and histopathology (kidney and liver) among high-dose animals (ECHA, 2012a).

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

Thus, the derived NOAEL for the repeated dose toxicity data is 55 mg/kg/day/3 or 18.3 mg/kg/day.

Therefore, the isobornyl methyl ether MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1-ethyl-3-methoxytricyclo[2.2.1.02,6]heptane NOAEL in mg/kg/day by the total systemic exposure to isobornyl methyl ether, 18.3/0.00023 or 79565.

In addition, the total systemic exposure to isobornyl methyl ether (0.23 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/01/2017.

10.1.3. Reproductive toxicity

The margin of exposure for isobornyl methyl ether is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on isobornyl methyl ether. Read-across material, isobornyl acetate (CAS # 125-12-2; see Section 5) has sufficient developmental toxicity data. In an OECD 414/GLP study, groups of 20 female Wistar rats were administered isobornyl acetate in a limit test once daily via oral gavage at a dose of 1000 mg/kg/day during gestation day (GD) 7–16. A group of 21 female rats, which was used as the control group, received the vehicle. Rats were euthanized on GD 21. No effects were seen in the clinical parameters, body weight, organ weights, and macroscopic examination of the organs (heart, liver, kidneys, and spleen). Ovaries and uterine content observations revealed no test material-related effects. The morphological examination of fetuses revealed no evidence for embryotoxic and teratogenic effects of the test material. Therefore, the NOAEL was considered to be 1000 mg/kg/day, the only dose tested for both maternal and developmental toxicity, based on the absence of test material-related toxic effects (ECHA, 2012b). Therefore, the isobornyl methyl ether MOE for the developmental toxicity endpoint can be calculated by dividing the isobornyl acetate NOAEL in mg/kg/day by the total systemic exposure to isobornyl methyl ether, 1000/0.00023 or 4347826.

There are no fertility data for isobornyl methyl ether. Read-across material, isobornyl acetate (CAS # 125-12-2; see Section 5) has sufficient fertility data. In an OECD 415/GLP oral gavage 1-generation reproduction toxicity study, groups of 25 Crl:CD (Sprague Dawley) rats/sex/dose were treated with 0, 30, 100, or 300 mg/kg/day of isobornyl acetate. Male rats were treated once daily 84 days before the cohabitation period, through the cohabitation period (maximum of 14 days), and until the day before euthanasia, for a total of 113–116 days. Female rats were treated once daily 14 days before the cohabitation period, through the cohabitation period (maximum of 14 days), and continuing through the day of euthanasia (day 25 of presumed gestation [for rats that do not deliver] or day 22 of lactation [for rats that delivered a litter]), for a total of approximately 53 or 74 days. Surviving parental males were euthanized after the completion of the cohabitation period (days 114 through 117 of study), and females were euthanized on day 22 or 25 of lactation. F1 generation animals were euthanized on days 57 through 63 postpartum. No mortality related to the test material occurred in the P and F1 generation rats. Clinical signs of toxicity (non-adverse) seen in parental animals consisted of a slight to moderate increase in salivation at ≥ 100 mg/kg/day in both sexes and low incidence of urine-stained abdominal fur in females at 300 mg/kg/day. There were no test material-related clinical signs in F1 generation rats. There were no test material-related effects on body weights (including terminal body weights), bodyweight gains, or feed consumption values (absolute [g/day] or relative [g/kg/day]) at any dose level in the P and F1 generation rats. There were no treatment-related effects on the reproductive parameters of the P generation rats or the development of the F1 generation offspring up to the highest dose tested. Based on the absence of any treatment-related adverse effects in all dose levels, the NOAEL for reproductive toxicity in the P generation rats and the NOAEL for viability and growth of the F1 generation offspring was considered to be 300 mg/kg/day, the highest dose tested (RIFM, 2011; RIFM, 2013; RIFM, 2017a). Based on the above results, the NOAEL for fertility was considered to be 300 mg/kg/day. **Therefore, the isobornyl methyl ether MOE for the fertility endpoint can be calculated by dividing the isobornyl acetate NOAEL in mg/kg/day by the total systemic exposure to isobornyl methyl ether, 300/0.00023 or 1304348.**

In addition, the total systemic exposure to isobornyl methyl ether (0.23 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/01/17.

10.1.4. Skin sensitization

Based on existing data and the application of DST, isobornyl methyl ether does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for isobornyl methyl ether or on any read-across materials. However, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1979).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentrations for isobornyl methyl ether that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/02/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, isobornyl methyl ether would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available

Table 1
Acceptable concentrations for isobornyl methyl ether that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Concentration in Finished Products
1	Products applied to the lips	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.01%
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.00%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.08%

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

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

10.2. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/12/17.

10.2.1. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level for isobornyl methyl ether is below the Cramer Class III TTC value for inhalation exposure local effects.

10.2.1.1. Risk assessment. There are no inhalation data available on isobornyl methyl ether. Based on the Creme RIFM Model, the inhalation exposure is 0.0017 mg/day. This exposure is 276 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/01/17.

10.3. Environmental endpoint summary

10.3.1. Screening-level assessment

A screening-level risk assessment of isobornyl methyl ether 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, isobornyl methyl ether 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 isobornyl methyl ether as possibly persistent but bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012c). 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.

10.3.2. Risk assessment

Based on the current Volume of Use (2015), isobornyl methyl ether presents a risk to the aquatic compartment in the screening-level assessment.

10.3.3. Key studies

10.3.3.1. Biodegradation. No data available.

10.3.3.2. Ecotoxicity. No data available.

10.3.4. Other available data

Isobornyl methyl ether has been pre-registered for REACH with no additional data at this time.

10.3.5. 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)	11.22			1,000,000	0.01122	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	5.59	3.66	4.93	10,000	0.366	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.39	2.39
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.366 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: 11/29/17.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110726.

Appendix

Read-across Justification

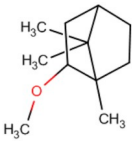
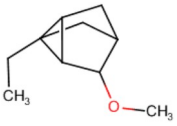
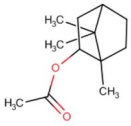
Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were

examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.

- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material
Principal Name	Isobornyl methyl ether	2-Ethyl-5-methoxybicyclo [2.2.1]heptane	Isobornyl acetate
CAS No.	5331-32-8	31996-78-8	125-12-2
Structure			
Similarity (Tanimoto Score)		0.66	0.73
Read-across Endpoint		• Genotoxicity • Repeated dose Toxicity	• Reproductive Toxicity
Molecular Formula	$C_{11}H_{20}O$	$C_{10}H_{18}O$	$C_{12}H_{20}O_2$
Molecular Weight	168.28	154.24	196.29
Melting Point (°C, EPI Suite)	13.61	6.74	34.11
Boiling Point (°C, EPI Suite)	182.22	170.12	225.89
Vapor Pressure (Pa @ 25 °C, EPI Suite)	159	277	14.3
Log Kow (KOWWIN v1.68 in EPI Suite)	3.55	3.2[1]	4.3
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	182.19	242	9.721
J_{max} (μg/cm^2/h, SAM)	39.312	489.312	81.82
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.15E-003	1.62E-003	4.37E-004
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Non-Carcinogen (low reliability)	• Non-Carcinogen (low reliability)	
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 v3.4)	• Non-binder, without OH or NH2 group		•Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)		• Non-toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (-OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

1. RIFM, 1989

Summary

There are insufficient toxicity data on isobornyl methyl ether (CAS # 5331-32-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2-ethyl-5-methoxybicyclo[2.2.1]heptane (CAS # 31996-78-8) and isobornyl acetate (CAS # 125-12-2) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 2-Ethyl-5-methoxybicyclo[2.2.1]heptane (CAS # 31996-78-8) was used as a read-across analog for the target material, isobornyl methyl ether (CAS # 5331-32-8) for the genotoxicity and repeated dose toxicity endpoints.
  - oThe target material and the read-across analog are structurally similar and belong to the class of aliphatic bicyclic ethers.
  - oThe target material and the read-across analog share a common saturated bicyclic structure.
  - oThe key structural difference between the target material and the read-across analog is that the target material has a dimethyl substitution on the bridge carbon whereas the read-across analog does not. The positions of the remaining methyl and methoxy substituents also differ. These structural differences are toxicologically insignificant.

oStructural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a common saturated bicyclic structure. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
oThe physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
oAccording to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
oThe target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
oThe structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Isobornyl acetate (CAS # 125-12-2) was used as a read-across analog for the target material isobornyl methyl ether (CAS # 5331-32-8) for the reproductive toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aliphatic bicyclic ethers and esters, respectively.
  - o The target material and the read-across analog share a common saturated bicyclic structure.
  - o The key structural difference between the target material and the read-across analog is that the target material is a methyl ether whereas the read-across analog is an acetate ester. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a common saturated bicyclic structure. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - o The target is shown to be a toxicant with good reliability by the CAESAR v2.1.6 model, while the read-across analog is shown to be a non-toxicant with low reliability by the same model. The data described for the read-across analog in the reproductive toxicity section show that the read-across material does not pose a concern under current exposure levels. The ER binding alert, which is another fertility toxicity indicator, is negative for both of the materials. Therefore, with the data for the read-across analog and the structural similarity between the read-across analog and the target material, the alert for the target material will be superseded by the data for read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

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

Q1. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene (see explanation in Cramer et al., 1978)? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **No**
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? **No**
Q26. Monocycloalkanone or a bicyclo compound? **No**
Q22. Common component of food? **No**
Q33. Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? **No, Class III (High)**

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