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Short review

RIFM fragrance ingredient safety assessment, *sec*-butyl ethyl ether, CAS Registry Number 2679-87-0

A.M. Api [a], D. Belsito [b], S. Biserta [a], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], S. Gadhia [a], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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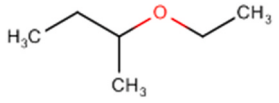
CAS Registry Number: 2679-87-0



Abbreviation/Definition List:

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2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 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.

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.

sec-Butyl ethyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *sec*-butyl ethyl ether is not genotoxic. Data on read-across analog diisopropyl ether (CAS # 108-20-3) provide a calculated margin of exposure (MOE) > 100 for the repeated dose, reproductive, and local respiratory toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *sec*-butyl ethyl ether is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; for the hazard assessment based on the screening data, *sec*-butyl ethyl ether is not persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, *sec*-butyl ethyl ether was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(Dakoulas, 2017; RIFM, 2019; RIFM, 2018)
Repeated Dose Toxicity: NOAEL = 3576 mg/kg/day.	(ECHA REACH Dossier: Diisopropyl Ether; ECHA, 2011)
Reproductive Toxicity: Developmental toxicity: NOAEL = 476 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Diisopropyl Ether; ECHA, 2011; Japanese Chemicals Collaborative Knowledge Database: Diisopropyl Ether; J-Check, 2019)
Skin Sensitization: Not a concern for skin sensitization at current, declared use levels; the exposure is below the DST.	
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 29700 mg/m^3.	(ECHA REACH Dossier: Diisopropyl Ether; ECHA, 2011)

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 2.96 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 9.095 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Not applicable

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. **Chemical Name:** *sec*-Butyl ethyl ether
2. **CAS Registry Number:** 2679-87-0
3. **Synonyms:** Butane, 2-ethoxy-; Ethyl *sec*-butyl ether; *sec*-Butyl ethyl ether
4. **Molecular Formula:** $C_6H_{14}O$
5. **Molecular Weight:** 102.17
6. **RIFM Number:** 6740
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 82.38 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.96 (EPI Suite)
4. **Melting Point**: 87.05 °C (EPI Suite)
5. **Water Solubility:** 2452 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 50 mm Hg at 20 °C (Fragrance Materials Association), 73.3 mm Hg at 20 °C (EPI Suite v4.0), 92.8 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:** A colorless liquid which has an extremely diffusive, fresh-fruity odor, somewhat fruity-oily

3. Volume of use (worldwide band)

1. <0.1 metric ton per year	IFRA (2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.000% (No reported use in hydroalcoholics)	RIFM (2017)
2. Inhalation Exposure*: 0.000000015 mg/kg/day or 0.0000011 mg/day	RIFM (2017)
3. Total Systemic Exposure:** 0.00000034 mg/kg/day	RIFM (2017)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
III	I	I

*See the Appendix below for details.

2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: Diisopropyl ether (CAS # 108-20-3)
   c. Reproductive Toxicity: Diisopropyl ether (CAS # 108-20-3)
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: Diisopropyl ether (CAS # 108-20-3)
   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

sec-Butyl ethyl ether is reported to occur in the following foods by the VCF*:

Citrus fruits.
Vinegar.
Wine.

*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

Pre-registered; no dossier available as of 07/12/19.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, *sec*-butyl ethyl ether does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. *sec*-Butyl ethyl ether was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of *sec*-butyl ethyl 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 *sec*-butyl ethyl 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 (Dakoulas, 2017). Under the conditions of the study, *sec*-butyl ethyl ether was not mutagenic in the Ames test.

The clastogenic activity of *sec*-butyl ethyl 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 *sec*-butyl ethyl ether in ethanol at concentrations up to 1020 μg/mL in a dose range finding (DRF) study and the micronuclei analysis in the presence and absence of metabolic activation. A statistically significant increase in the frequency of micronucleated binucleated (MNBN) cells was observed at 300 μg/mL (mid-dose) in the 4-h treatment without S9, with no dose response. Therefore, 2 additional doses of 150 and 600 μg/mL were included in the microscopic evaluation. Statistically significant increases in micronuclei induction were observed at 150 and 600 μg/mL; however, the Cochran-Armitage test was still negative for a dose response. Therefore, the micronucleus assay was repeated in the 4-h treatment without S9 at the same concentrations. In the repeat micronucleus assay, statistically significant and dose-dependent increases in micronuclei induction were observed at doses 300 and 1020 μg/mL, respectively. Based on these findings, *sec*-butyl ethyl ether was concluded to be positive for the induction of micronuclei in the *in vitro* mammalian cell micronucleus test (RIFM, 2019). Under the conditions of the study, *sec*-butyl ethyl ether was considered to be clastogenic in the *in vitro* micronucleus test. A follow-up *in vivo* micronucleus study was conducted in mice.

The clastogenic activity of *sec*-butyl ethyl ether was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female Hsd:ICR (CD-1) mice. Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized at 48 h, and the bone marrow was extracted and examined for reticulocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated reticulocytes in the bone marrow (RIFM, 2018). Under

the conditions of the study, *sec*-butyl ethyl ether was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, *sec*-butyl ethyl ether does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/12/19.

11.1.2. Repeated dose toxicity

The MOE for *sec*-butyl ethyl ether is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *sec*-butyl ethyl ether. Read-across material diisopropyl ether (CAS # 108-20-3; see section VI) has sufficient repeated dose toxicity data. In a study equivalent to OECD TG 413, groups of 14 Sprague Dawley Tac:N (SD)fBR rats/sex/dose were administered the test material diisopropyl ether at doses of 0 (untreated control), 0 (sham-exposed), 480, 3300, or 7100 ppm for 6 h/day 5 days/week for 13 weeks through whole-body inhalation. The doses were equivalent to 520, 3576, or 7694 mg/kg/day according to standard minute volume and body weight parameters for Sprague Dawley rats. High-dose males were reported to have hepatocellular hypertrophy associated with significantly increased absolute liver weights (39%) and absolute kidney weights; the kidneys showed an increased incidence of hyaline droplets in the proximal tubules. However, the presence of hyaline droplets was not confirmed by immunohistochemistry or other staining methods. High-dose females had statistically significant increases in absolute weights of liver (18%) and kidneys; however, increased kidney weights were not associated with any microscopic changes. Mid-dose males showed significant increases in absolute weights of the liver and kidneys. Mid-dose females showed significant increases in absolute weights of the liver only. The NOAEL for the study was considered to be 3300 ppm or 3576 mg/kg/day based on the increase in liver and kidney weights in high-dose animals (ECHA, 2011).

In another study, groups of 12 rats/sex/dose at doses of 0 (olive oil), 100, 300, 1000 mg/kg/day. The study was conducted in accordance with GLP/OECD 422 guidelines. The males were treated for 42 days whereas the females were treated from 14 days before mating to day 4 of lactation. Liver weights among mid- and high-dose males and kidney weights among high-dose males were increased. Histopathological examination revealed centrilobular hepatocyte hypertrophy among high-dose males. Eosinophilic bodies in the proximal tubule of the kidneys appeared among treated males, while regeneration of the proximal tubule occurred in mid- and high-dose males. The NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (J-Check, 2019).

The most conservative NOAEL of 3576 mg/kg/day from the 13-week inhalation study on diisopropyl ether was considered for the safety assessment of *sec*-butyl ethyl ether.

Therefore, the *sec*-butyl ethyl ether MOE for the repeated dose toxicity endpoint can be calculated by dividing the diisopropyl ether NOAEL by the total systemic exposure to *sec*-butyl ethyl ether, 3576/0.00000034, or 10517647059.

In addition, the total systemic exposure to *sec*-butyl ethyl ether (0.00034 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: ECHA, 2011; US EPA, 2006.

Literature Search and Risk Assessment Completed On: 08/12/19.

11.1.3. Reproductive toxicity

The MOE for *sec*-butyl ethyl ether 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 *sec*-butyl ethyl ether. Read-across material diisopropyl ether (CAS # 108-20-3; see section VI) has sufficient reproductive toxicity data.

In an OECD 422/GLP study, the test material diisopropyl ether was administered via oral gavage to groups of 12 Crl:CD(SD) rats/sex/dose at doses of 0, 100, 300, or 1000 mg/kg/day in olive oil. Males were treated for 42 days, while females were treated from 14 days prior to mating up to day 4 of lactation. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups and were not mated. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. There were no treatment-related adverse effects observed on the estrous cycle, copulation, fertility, delivery or lactation, and growth and development of pups in any of the treated animals. Thus, the NOAEL for reproductive toxicity (fertility and developmental toxicity) was considered to be 1000 mg/kg/day, the highest dose tested (J-Check, 2019). **Therefore, the diisopropyl ether MOE for the fertility endpoint can be calculated by dividing the *sec*-butyl ethyl ether NOAEL in mg/kg/day by the total systemic exposure to diisopropyl ether, 1000/0.00000034, or 2941176471.**

In a prenatal developmental toxicity study (similar to OECD 414 and non-GLP), 22 pregnant female Sprague Dawley rats/group were exposed to diisopropyl ether via inhalation (whole-body exposure) at concentrations of 0 (untreated), 0 (sham-exposed), 430, 3095, or 6745 ppm (equivalent to 0, 476, 3423, 7461 mg/kg/day, respectively, as per standard minute volume and body weight for female Sprague Dawley rats) for 6 h per day for gestation days (GDs) 6–15. Significant decreases in bodyweight gain were reported in the mid- and high-exposure groups on GDs 0–20. Food consumption was significantly decreased in comparison to untreated and sham-exposed controls in both the mid- and high-exposure groups throughout GDs 6–16. Reproductive parameters (number of pregnant females, percent preimplantation loss, percent resorptions, and litter sizes) and fetal body weights were not affected by exposure. Fetal skeletal examination revealed a significant increase in rudimentary (small, discrete ossification) or short (less than one-half the length of the preceding rib) fourteenth ribs in fetuses of the mid- and high-exposure groups. All observed fourteenth ribs were rudimentary except in 2 fetuses from each of the mid- and high-exposure groups that had either bilateral short fourteenth ribs or bilateral short and rudimentary fourteenth ribs. No other treatment-related findings were reported during fetal examinations. The NOAEC for maternal toxicity was considered to be 430 ppm or 476 mg/kg/day, based on decreased body weight and food consumption among the mid- and high-exposure group dams. The NOAEC for developmental toxicity was considered to be 430 ppm or 476 mg/kg/day, based on increased incidences of skeletal alterations among the mid- and high-exposure group fetuses (ECHA, 2011).

The most conservative developmental toxicity NOAEL of 476 mg/kg/day from the prenatal developmental toxicity study was selected for the developmental toxicity endpoint. **Therefore, the diisopropyl ether MOE for the developmental toxicity endpoint can be calculated by dividing the *sec*-butyl ethyl ether NOAEL in mg/kg/day by the total systemic exposure to diisopropyl ether, 476/0.00000034, or 1400000000.**

In addition, the total systemic exposure to *sec*-butyl ethyl ether (0.00034 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 08/16/19.

11.1.4. Skin sensitization

Based on the application of DST, *sec*-butyl ethyl ether does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for *sec*-butyl ethyl ether. Due to the absence of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 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 maximum acceptable concentrations for *sec*-butyl ethyl ether that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/23/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *sec*-butyl ethyl ether would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Maximum acceptable concentrations for *sec*-butyl ethyl ether that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	NRU[b]
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	NRU[b]
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	NRU[b]
10	Household care products with mostly hand contact	2.7%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	NRU[b]

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *sec*-butyl ethyl ether in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, *sec*-butyl ethyl ether 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: 07/22/19.

11.1.6. Local respiratory toxicity

There are insufficient inhalation data available on *sec*-butyl ethyl ether; however, in a subchronic 13-week inhalation study for the read-across analog diisopropyl ether (CAS # 108-20-3; see section VI), a NOAEC of 29700 mg/m^3 was reported (ECHA, 2011).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 13-week inhalation study equivalent to OECD TG 413, 14 male and female Sprague Dawley derived Tac:N(SD) fBR rats per group were exposed to diisopropyl ether vapor via whole-body inhalation exposure (ECHA, 2011). The exposure groups were 2 controls (untreated and sham-exposed) with 0, 2000, 13800, and 29700 mg/m^3 of the test material. Standard observations included bodyweight changes, clinical observations, hematology, clinical chemistry, gross pathology, and histopathology for all major tissues including lungs and nasal turbinates. The only histopathology observed was in the liver and kidney of the high-exposure group males. No effects were observed in any other organs evaluated for histopathology, including nasal turbinates and lungs. Therefore, based on the observations, the NOAEC for local respiratory toxicity was identified at the highest exposure concentration of 29700 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (29700 mg/m^3) × (1 m^3/1000L) = 29.7 mg/L
- MV of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (29.7 mg/L) × (61.2 L/day) = 1817.6 mg/day
- (1817.6 mg/day)/(0.0016 kg lung weight of rat*) = 1136000 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0000011 mg/day; this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; Safford, 2015a). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.00000169 mg/kg lung weight/day, resulting in an MOE of 672,189,349,112 (i.e., [1136000 mg/kg lung weight of rat/day]/[0.00000169 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0000011 mg/day is deemed to be

safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Marsh (1950).

Literature Search and Risk Assessment Completed On: 08/16/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *sec*-butyl ethyl ether 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, *sec*-butyl ethyl ether was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify *sec*-butyl ethyl ether 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 $\geq$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

Not applicable.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. sec-Butyl ethyl ether has been pre-registered under REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 07/23/19.

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&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 01/31/20.

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

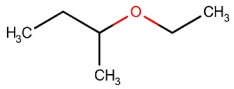
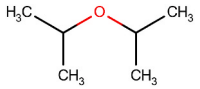
Read-across Justification

Methods

The read-across analog was 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
Principal Name	*sec*-Butyl ethyl ether	Isopropyl ether
CAS No.	2679-87-0	108-20-3
Structure		
Similarity (Tanimoto Score)		0.71
Read-across Endpoint		• Reproductive Toxicity • Repeated Dose Toxicity • Local Respiratory toxicity
Molecular Formula	$C_6H_{14}O$	$C_6H_{14}O$
Molecular Weight	102.17	102.17
Melting Point (°C, EPI Suite)	−87.05	−86.8
Boiling Point (°C, EPI Suite)	81.00	68.5
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.24E+004	1.99E+004
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.96	1.52
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2452	5800
J_{max} (μg/cm^2/h, SAM)	548.176	196.768
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.72E+002	2.59E+002
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)	• Toxicant (good reliability)
Local Respiratory toxicity		
Respiratory sensitization (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• No metabolites	• No metabolites

Summary

There are insufficient toxicity data on *sec*-butyl ethyl ether (CAS # 2679-87-0). 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, isopropyl ether (CAS # 108-20-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Isopropyl ether (CAS # 108-20-3) was used as a read-across analog for the target material *sec*-butyl ethyl ether (CAS # 2679-87-0) for the reproductive toxicity, repeated dose toxicity, and local respiratory toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of branched saturated ethers.
  - o The target material and the read-across analog are structural isomers.
  - o The key difference between the target material and the read-across analog is that the target material has *sec*-butyl and ethyl branches whereas the read-across analog has 2 isopropyl branches. 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

- o 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 show that the MOE is adequate at the current level of use. The predictions are superseded by the data.
- 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 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? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? 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, High (Class III)

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