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Short Review

RIFM fragrance ingredient safety assessment, 1,4-bis(ethoxymethyl)cyclohexane, CAS Registry Number 54889-63-3

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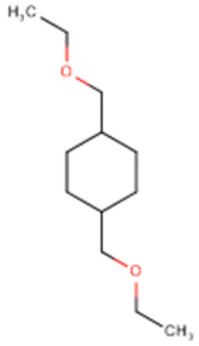

Name: 1,4-Bis(ethoxymethyl)cyclohexane
CAS Registry Number: 54889-63-3

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024) 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
LOEL - Lowest Observed 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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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

(*continued on next column*)

(*continued*)

Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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.

1,4-Bis(ethoxymethyl)cyclohexane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 1,4-bis(ethoxymethyl)cyclohexane is not genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints, and show that there are no safety concerns for 1,4-bis(ethoxymethyl) cyclohexane for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on structural analysis. There is no chromophore present in the structure of 1,4-bis(ethoxymethyl) cyclohexane, so UV (ultraviolet) absorbance is not possible, and 1,4-bis(ethoxymethyl)cyclohexane does not present a concern for photoirritation or photoallergenicity. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 1,4-bis(ethoxymethyl)cyclohexane is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 1,4-bis(ethoxymethyl)cyclohexane was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2013b; RIFM, 2016e)
Repeated Dose Toxicity: NOAEL = 5 mg/kg/day. RIFM (2016a)
Reproductive Toxicity: NOAEL = 15 mg/kg/day. RIFM (2016a)
Skin Sensitization: No concern for skin sensitization. RIFM (2013c)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 0% (OECD 302C) RIFM (2016d)
Bioaccumulation:
Critical Measured Value: 234 L/kg (OECD 305) RIFM (2018)
Ecotoxicity:
Screening-level: 48-h *Daphnia* LC50: 5.2 mg/L (ECOSAR v2.0; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia* LC50: 5.2 mg/L (ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 0.52 µg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1

1. Identification

1. **Chemical Name:** 1,4-Bis(ethoxymethyl)cyclohexane
2. **CAS Registry Number:** 54889-63-3
3. **Synonyms:** Pear ether 97; Vertofruct; 1,4-Bis(ethoxymethyl)cyclohexane 97%; 1,4-Bis(ethoxymethyl)-cyclohexane; 1,4-Bis(ethoxymethyl)cyclohexane
4. **Molecular Formula:** $C_{12}H_{24}O_2$
5. **Molecular Weight:** 200.32 g/mol
6. **RIFM Number:** 1459
7. **Stereochemistry:** No stereocenter is present, and no stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 247.33 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** ~3 (estimated from the single solubilities in n-octanol and in water due to the fact that the test material is surface active) (RIFM, 2014b), 3.46 (EPI Suite v4.11)
4. **Melting Point**: 15.10 °C (EPI Suite v4.11)
5. **Water Solubility:** 48.18 mg/L at 25 °C (EPI Suite v4.11), 569 ± 7 mg/L at 20 ± 0.5 °C (RIFM, 2013a)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0505 mm Hg (EPI Suite v4.11)
8. **UV Spectra:** Not Available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2019)

4. exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.5)

1. **95**th **Percentile Concentration in Showergel:** 0.013% (RIFM, 2021)

(No Recorded use in Fine Fragrance)

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00069 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024).

**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 et al., 2015, 2017; Safford et al., 2015, 2017, 2024).

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	Toxtree v3.1	OECD QSAR Toolbox v4.6 (OECD, 2023)
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

1,4-Bis(ethoxymethyl)cyclohexane is not reported to occur in foods by the VCF*.

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

9. Reach dossier

Available (ECHA, 2015); accessed on 10/19/23.

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, 1,4-bis(ethoxymethyl)cyclohexane does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1,4-bis(ethoxymethyl)cyclohexane 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1,4-bis(ethoxymethyl)cyclohexane in dimethyl sulfoxide 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, 2013b). Under the conditions of the study, 1,4-bis(ethoxymethyl)cyclohexane was not mutagenic in the Ames test.

The clastogenic activity of 1,4-bis(ethoxymethyl)cyclohexane was evaluated in an *in vitro* micronucleus test conducted in compliance with

GLP regulations and in accordance with OECD TG 487. V79 cells derived from the Chinese hamster were treated with 1,4-bis(ethoxymethyl) cyclohexane in ethanol at concentrations up to 500 μg/mL in the initial experiments (experiments 1 and 2) in the presence or absence of S9; confirmatory micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence of S9 (experiments 3 and 4). The micronucleus rates partly exceeded both the range of the 95% control limit of the historical negative control data (0.0%–1.0% micronucleated cells) and the range of the historical negative control data (0.1%–1.5% micronucleated cells) in the presence of metabolic activation at concentrations of 62.5, 125.0, 250.0 μg/mL (1.3%, 1.4%, and 0.9% micronucleated cells, respectively) in the 4-h treatment with a 24-h exposure time in experiment 1, and at concentrations of 62.5, 125.0, and 250.0 μg/mL (1.7%, 1.6%, and 2.0% micronucleated cells, respectively) in the 4-h treatment with a 44-h exposure time in experiment 2. Repeat experiments were performed to corroborate these data. The test material assessed concentrations ranging from 50.0 to 300.0 μg/mL in the repeat 4-h treatment with a 24-h exposure time in the presence of S9 in experiment 3. A dose-related increase in micronucleated cells was observed at 75.0, 100.0, and 150.0 μg/mL (0.5%, 0.8%, and 1.1%). No statistical significance compared to the respective vehicle control value (0.7% micronucleated cells) occurred, and all values were close to the 95% control limit of the historical negative control data (0.0%–1.0% micronucleated cells) and clearly within the historical negative control data range (0.1%–1.5% micronucleated cells). In experiment 4, the test material assessed concentrations ranging from 50.0 to 300.0 μg/mL in the repeat 4-h treatment with a 44-h exposure time in the presence of S9. A statistically significant increase in the frequency of micronucleated binucleated (MNBN) cells was observed at 100.0, 150.0, and 200.0 μg/mL (1.1%, 1.3%, and 1.2%) in the 4-h treatment with a 44-h exposure time in the presence of S9. However, the MNBN frequencies (0.8%–1.3% micronucleated cells) at these concentrations were within or close to the range of the 95% control limit of the historical negative control data (0.0%–1.0% micronucleated cells) and clearly within the historical negative control data range (0.1%–1.5% micronucleated cells). Therefore, the statistically significant increases at these concentrations were considered biologically non-relevant and not indicative of clastogenic effects. Based on these findings, 1,4-bis(ethoxymethyl)cyclohexane was negative for the induction of micronuclei under *in vitro* conditions in V79 cells in either the presence or absence of S9 (RIFM, 2016e). Under the conditions of the study, 1,4-bis(ethoxymethyl)cyclohexane was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 1,4-bis(ethoxymethyl)cyclohexane does not present a concern for genotoxic potential.

Additional References: RIFM, 2016f.

Literature Search and Risk Assessment Completed On: 01/05/24.

11.1.2. Repeated dose toxicity

The MOE for 1,4-bis(ethoxymethyl)cyclohexane is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1,4-bis(ethoxymethyl)cyclohexane.

In a GLP- and OECD 415-compliant study, groups of 25 Wistar rats/sex/dose were administered 1,4-bis(ethoxymethyl)cyclohexane via oral gavage at doses of 0, 5, 15, or 50 mg/kg/day for at least 69 days (i.e., prior to mating and up until one day prior to euthanasia). Females were euthanized 123 or 126 days after the start of treatment, and male animals were euthanized after 100 or 105 days. There were no treatment-related mortalities observed throughout the study. However, 2 female rats at the highest dose were found dead on postnatal days (PNDs) 11 and 15, showing signs of substance aspiration. One control female was euthanized on PND 6 due to severe labored respiration, noisy breathing, and piloerection. Salivation occurred in treated animals. One female at the highest dose showed blood in the bedding on gestational day (GD) 23. Food consumption was significantly decreased in high-dose females during lactation and PNDs 1−21. This coincided with a decrease in mean body weight on GD 20 and PND 4–14 and decreased bodyweight gain during GD 20. Significantly lower mean body weights were also observed in the mid-dose females during gestation and lactation, along with decreased bodyweight gain during gestation. Gross pathology of female rats at the highest dose showed a minimal increase in the incidence of foci in the glandular stomach that corresponded to histopathological changes, including stomach ulcers and erosions. Red discoloration and foamy content were observed in the lungs of 2 spontaneously deceased female rats at the high dose. Organ weight changes in male rats included a significant decrease in absolute (mid and high doses) and relative seminal vesicle weight (mid dose only) in male rats; however, this was not considered adverse as it was not dose-dependent and was within the historical control range. There was a significant increase in relative kidney weight in male rats at the high dose. Finally, there was a significant decrease in absolute spleen weight at the mid and high doses. Histology of the left testis revealed increased tubular degeneration at the highest dose and coincided with some tubules showing partially depleted germ cells. However, the depletion of germ cells sometimes only affected a focal region within a small proportion of tubular cross-sections, and the severity was minimal in all cases. Since these findings did not coincide with a change in testis weight, findings in the epididymis, or changes in sperm parameters (i.e., count, motility, morphology), they were attributed to the treatment but were not considered adverse. Additionally, 2 control male rats also showed incidental tubular degeneration, but the germ cell depletion showed a different distribution pattern. Organ weight changes in female rats included a significant increase in absolute adrenal gland weights at the low and high doses and a significant increase in relative adrenal gland weight at the highest dose. However, these changes did not correspond to any histological changes, so it was considered incidental. The ovaries had a significant decrease in absolute and relative weight at the high dose, but histology did not show any correlated findings, and it was considered an incidental finding. The liver showed a significant increase in relative weight at the highest dose. However, this change was within a historical control range, and there were no changes to clinical biochemistry, so it was not considered adverse. Additionally, macroscopic findings of the liver in the high-dose females (2/25 animals) showed one female with a focus on the liver and another with a focal constriction. Upon histological examination, these findings correlated to necrosis and fibrosis, respectively. Histology revealed minimal erosion/ulceration in the glandular stomach of a few high-dose females. A female rat at the high dose that spontaneously died showed slight congestion in the lungs along with slight alveolar edema and histiocytosis. Clinical chemistry showed a significant decrease in total protein, albumin, globulin, and calcium levels and a significant increase in inorganic phosphate levels in male rats at the high dose. These differences were considered incidental because they were within historical control ranges or were close to the control mean. Additionally, in male rats at the mid dose, creatinine values were lower compared to controls, but the change was not dose-dependent. Female rats showed increased mean corpuscular volume (MCV) at the mid and high doses. However, MCV is calculated using red blood cell parameters (i.e., red blood cell count, hematocrit, hemoglobin values), but these parameters were not altered. Therefore, the MCV change was considered incidental. Thus, based on the reduced food consumption and mean body weight in female rats at 50 mg/kg/day and significantly lower mean body weight in females at 15 mg/kg/day, the repeated dose toxicity NOAEL for this study was determined to be 5 mg/kg/day (RIFM, 2016a).

Therefore, the 1,4-bis(ethoxymethyl)cyclohexane MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1,4-bis(ethoxymethyl)cyclohexane NOAEL in mg/kg/day by the total systemic exposure to 1,4-bis(ethoxymethyl)cyclohexane, 5/0.00069 or 7246.

Additionally, the total systemic exposure to 1,4-bis(ethoxymethyl)

cyclohexane (0.69 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: None.

Literature Search and Risk Assessment Completed On: 01/03/24.

11.1.3. Reproductive toxicity

The MOE for 1,4-bis(ethoxymethyl)cyclohexane is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 1,4-bis(ethoxymethyl)cyclohexane.

In a GLP- and OECD 415-compliant study, groups of 25 Wistar rats/sex/dose were administered 1,4-Bis(ethoxymethyl)cyclohexane via oral gavage at doses of 0, 5, 15, or 50 mg/kg/day for at least 69 days (i.e., prior to mating and up until one day prior to euthanasia). Females were euthanized 123 or 126 days after the start of treatment, and male animals were euthanized after 100 or 105 days. Females were not dosed during labor. There were no treatment-related mortalities observed throughout the study. However, 2 female rats at the highest dose were found dead on PNDs 11 and 15, showing signs of substance aspiration. One control female was euthanized on PND 6 due to severe labored respiration, noisy breathing, and piloerection. Dose-dependent salivation occurred in treated animals, with the highest incidence and severity occurring at the highest dose. One female at the highest dose showed blood in the bedding on gestational day 23. Food consumption was significantly decreased in high-dose females during lactation and PNDs 1–21. This coincided with a decrease in mean body weight on gestational day 20 and PNDs 4–14 and decreased bodyweight gain during gestational day 20. Significantly lower mean body weights in the mid-dose females during gestation and lactation, along with decreased bodyweight gain during gestation, were observed. In high-dose group pups, significantly decreased mean body weight during PNDs 7−21 and decreased bodyweight gain during PNDs 4−21 were observed. Organ weight changes in pups of both sexes included a significant increase in absolute spleen and thymus weights, decreased relative spleen weight, and increased relative brain weight at the highest dose. These changes were considered a secondary effect of the lower pup body weights. In terms of developmental toxicity, at the mid dose, the pups showed slightly decreased pre-weaning body weights and weight gain that corresponded to decreased food consumption/bodyweight gain in the parental female rats. At the highest dose, the pups had significantly reduced body weights and gained less body weight compared to the control pups from PND 4 to weaning. This resulted in the pups having a weight that was slightly below the historical control range for pups at a comparable age, and so it was regarded as a delay in postnatal development. Thus, based on the reduced body weight and gain at 50 mg/kg/day, the developmental toxicity NOAEL for this study was determined to be 15 mg/kg/day (RIFM, 2016a).

In terms of fertility, there were fewer implantation sites in all dose groups, which coincided with a significantly lower number of pups delivered (total and liveborn) compared to the control. However, the number of stillborn pups was not significantly different from the control across all doses. There were no correlating morphological changes to the ovaries (i.e., number and appearance of primordial and growing follicles), uteri, or oviducts. Two sperm-positive female rats at the high dose and one in the mid dose did not deliver pups. The testis was considered a target of the treatment. Histology of the parental male rats revealed increased tubular degeneration in the left testis at the highest dose (9 out of 25 males), and it coincided with some tubules showing partially depleted germ cells. However, the depletion of germ cells sometimes only affected a focal region within a small proportion of tubular cross-sections, and the severity was minimal in all cases. Since these findings did not coincide with a change in testis weight, findings in the epididymis, or changes in sperm parameters (i.e., count, motility, morphology), they were attributed to the treatment but were not considered adverse. Additionally, 2 control male rats also showed incidental tubular degeneration, but the germ cell depletion showed a different distribution pattern. Thus, based on effects on the testis (i.e., tubular degeneration, germ cell depletion) and reduced implantation sites that resulted in the lower number of pups/live pups at 50 mg/kg/day, the fertility NOAEL for this study was determined to be 15 mg/kg/day (RIFM, 2016a).

Therefore, the 1,4-bis(ethoxymethyl)cyclohexane MOE for the developmental toxicity endpoint can be calculated by dividing the 1,4-bis(ethoxymethyl)cyclohexane NOAEL in mg/kg/day by the total systemic exposure to 1,4-bis(ethoxymethyl)cyclohexane, 15/0.00069 or 21739.

Therefore, the 1,4-bis(ethoxymethyl)cyclohexane MOE for the fertility endpoint can be calculated by dividing the 1,4-bis(ethoxymethyl)cyclohexane NOAEL in mg/kg/day by the total systemic exposure to 1,4-bis(ethoxymethyl)cyclohexane, 15/0.0069 or 21739.

Additionally, the total systemic exposure to 1,4-bis(ethoxymethyl) cyclohexane (0.69 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 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: 01/03/24.

11.1.4. Skin sensitization

Based on the existing data, 1,4-bis(ethoxymethyl)cyclohexane presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, 1,4-bis(ethoxymethyl)cyclohexane is not considered a skin sensitizer. The data are summarized in Table 1. This material is predicted *in silico* to be non-reactive with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.6). In a murine local lymph node assay (LLNA), 1,4-bis (ethoxymethyl)cyclohexane was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (RIFM, 2013c).

Based on the weight of evidence (WoE) from structural analysis and an animal study, 1,4-bis(ethoxymethyl)cyclohexane does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/23.

11.1.5. Photoirritation/photoallergenicity

Based on structural analysis, 1,4-bis(ethoxymethyl)cyclohexane would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photosafety studies available for 1,4-bis(ethoxymethyl)cyclohexane in experimental models. UV/Vis absorption spectra are not available. Structural analysis of 1,4-bis(ethoxymethyl)cyclohexane revealed that a chromophore is not present. Without a chromophore present, absorbance of UV/Vis light is not possible. Based on the lack of a chromophore, 1,4-bis(ethoxymethyl) cyclohexane does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra were not available. Structural analysis of the material revealed that a chromophore is not present. Without a chromophore, absorbance of UV/Vis light is not possible.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/12/23.

Table 1
Summary of existing data on 1,4-bis(ethoxymethyl)cyclohexane.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm^2	NOEL-HMT (induction) µg/cm^2	LOEL (induction) µg/cm^2	WoE NESIL µg/cm^2	LLNA[2] Weighted Mean EC3 Value µg/cm^2	GPMT	Buehler
No evidence of sensitization[3]	N/A	N/A	N/A	N/A	Negative up to 25000 (100%)	N/A	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.6)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	Radical reactions; Schiff base formation	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
[3]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1,4-bis(ethoxymethyl)cyclohexane is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 1,4-bis(ethoxymethyl)cyclohexane. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 4700 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: RIFM, 2016b.

Literature Search and Risk Assessment Completed On: 01/02/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1,4-bis(ethoxymethyl)cyclohexane 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1, 4-bis(ethoxymethyl)cyclohexane 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 v4.11 (US EPA, 2012a) did not identify 1,4-bis(ethoxymethyl)cyclohexane as possibly being 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 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, 2017). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 1,4-bis (ethoxymethyl)cyclohexane presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2014a:** Biodegradation of the test material was evaluated in a modified MITI according to the OECD 301C method. The amount of residual test material was determined using capillary gas chromatography (GC) analysis at the start and end of exposure to determine primary biodegradation. Calculations for biodegradability based on BOD, DOC, and residual test material were taken from the OECD guidelines. Under the conditions of this study, a mean of −1% biodegradation by BOD, −0.3% by DOC, and 1.1% was observed after 28 days.

RIFM, 2016d: The inherent biodegradability of the test material was evaluated in a modified MITI test according to the OECD 302C method. Under the conditions of this study, 4% and −1% biodegradation was observed after 28 days based on BOD and GC analysis, respectively.

RIFM, 2018: Bioconcentration potential of 14C 1,4-bis((ethoxymethyl)cyclohexane in zebrafish (*Danio rerio*) was evaluated according to the OECD 305 method. The fish were exposed to 1 control group and 2 treatment groups of test material at 0.1 and 1 μg/L in a flow-through system for an uptake period of 14 days followed by a depuration period. The overall BCF (growth-corrected kinetic BCF normalized to 5% lipid content) was reported to be 234 L/kg for the whole fish based on the total radioactive residues of the test material.

11.2.1.2.2. Ecotoxicity. **RIFM, 2016c:** An acute fish (*Gobiocypris rarus*) toxicity study was conducted according to the OECD 203 method under semi-static conditions. Under the conditions of this study, the 96-h LC50 was 81.5 mg/L. The maximum mean measured concentration caused no mortality, and the minimum mean was measured.

RIFM, 2014c: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static, closed vessel conditions. Under the conditions of this study and based on nominal concentrations, the 48-h EC50 was 71.2 (95% CI: 60.9−83.1) mg/L.

RIFM, 2015: An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of this study, and based on geometric mean measured concentrations, the EC50 for growth rate and yield was 101 and 61.5 mg/L, respectively.

11.2.1.2.3. Other available data. 1,4-Bis(ethoxymethyl)cyclohexane has been registered under REACH, with no additional data at this time.

11.2.1.3. Risk assessment refinement. Since 1,4-bis(ethoxymethyl)cyclohexane has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivations.

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)**	36.9			1000000	0.0369	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	8.004	5.202	6.771	10000	0.5202	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.0	3.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	1–10	1–10
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 0.52 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 VoU.

Literature Search and Risk Assessment Completed On: 12/07/23.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 06/28/24.

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.

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