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Short Review

# RIFM fragrance ingredient safety assessment, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene, CAS registry number 90530-04-4

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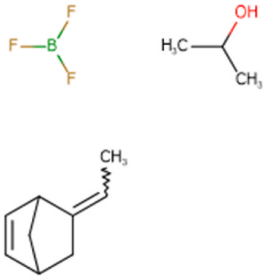

Name: 2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene CAS Registry Number: 90530-04-4

**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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 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; 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
**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
**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

(*continued on next column*)

(*continued*)

**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.**

2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). 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 photoirritation endpoint was evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1] hept-2-ene is not photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis spectra; 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene is not expected to be photoallergenic. The environmental endpoints were evaluated; 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene 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, 2017a; RIFM, 2017b)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** No safety concerns at the current declared use levels. Exposure is below the DST.
**Photoirritation/Photoallergenicity:** Not photoirritating/not expected to be photoallergenic. (UV/Vis Spectra, RIFM Database; RIFM, 1980a)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Screening-level: 2.8 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:**
Screening-level: 101.5 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Screening-level: Fish LC50: 15.05 mg/L (Salvito et al., 2002)
**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:** Fish LC50: 15.05 mg/L (Salvito et al., 2002)
**RIFM PNEC is:** 0.01505 μg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America (no VoU) and Europe: Not applicable; cleared at the screening-level

## 1. Identification

1. **Chemical Name:** 2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene
2. **CAS Registry Number:** 90530-04-4
3. **Synonyms:** Isoproxen; 2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene
4. **Molecular Formula:** $C_9H_{12}.C_3H_8O.BF_3$
5. **Molecular Weight:** 166.26 g/mol
6. **RIFM Number:** 5589
7. **Stereochemistry:** Isomer not specified. One stereocenter and a total of 2 stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 192.32 °C (EPI Suite v4.11)
2. **Flash Point:** 74 °C (Globally Harmonized System)
3. **Log $K_{OW}$:** 3.55 (EPI Suite v4.11)
4. **Melting Point**: −5.88 °C (EPI Suite v4.11)
5. **Water Solubility:** 60.02 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.744 mm Hg at 25 °C (EPI Suite v4.11), 0.518 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

## 3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Air Fresh Aerosol:** 0.052% (RIFM, 2021)
   (No Reported Use in Fine Fragrance)
2. **Inhalation Exposure*:** 0.000014 mg/kg/day or 0.0015 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0013 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; B. Safford et al., 2015; B. Safford et al., 2024; B. 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 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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; and Comiskey et al., 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 | 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

2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene 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

2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene has been pre-registered for 2010; no dossier available as of 03/18/24.

## 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, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene does not present a concern for genotoxicity.

*11.1.1.1. Risk Assessment.* 2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with metabolic activation, negative for cytotoxicity without metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were

treated with 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene in dimethylformamide (DMF) 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, 2017a). Under the conditions of the study, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene was not mutagenic in the Ames test.

The clastogenic activity of 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene in DMF at concentrations up to 1200 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h 2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017b). Under the conditions of the study, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/01/23.

*11.1.2. Repeated Dose Toxicity*

There are insufficient repeated dose toxicity data on 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene or any read-across materials. The total systemic exposure to 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

*11.1.2.1. Risk Assessment.* There are no repeated dose toxicity data on 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene (1.3 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 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:** 08/24/23.

*11.1.3. Reproductive Toxicity*

There are insufficient reproductive toxicity data on 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1] hept-2-ene or any read-across materials. The total systemic exposure to 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

*11.1.3.1. Risk Assessment.* There are no reproductive toxicity data on 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene (1.3 μg/kg/day) is below the TTC (1.5 μg/kg/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:** 08/24/23.

*11.1.4. Skin Sensitization*

Based on existing data and the application of DST, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1] hept-2-ene does not present a safety concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk Assessment.* Limited skin sensitization data are available for reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.6). In guinea pigs, a Buehler test did not present reactions indicative of sensitization (RIFM, 1980b). Additionally, in multiple confirmation of no induction in humans (CNIH) tests with either 2500 μg/cm$^2$, 15000 μg/cm$^2$, 16071 μg/cm$^2$, or 7500 μg/cm$^2$ of 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 54, 48, 47 or 49 volunteers in the respective studies (RIFM, 1980c; RIFM, 1981b; RIFM, 1981a; RIFM, 1982). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm$^2$ (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford 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 2 provides the supported concentrations for 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent supported 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:** 08/14/23.

*11.1.5. Photoirritation/Photoallergenicity*

Based on the available UV/Vis absorption spectra and human study data, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectrum 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene would not be expected to present a concern for photoallergenicity.

*11.1.5.1. Risk Assessment.* 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 photoirritation and photoallergenicity (Henry et al., 2009). In a human photoirritation study, 5% 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene in alcohol was not photoirritating to humans (RIFM, 1980a). Based on the available human study data and the lack of absorbance, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene does not present a concern for photoirritation. Based on lack of absorbance, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene does not present a concern for photoallergenicity.

*11.1.5.2. UV Spectra Analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark

**Table 1**
Summary of existing data on 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene.

| WoE Skin Sensitization Potency Category[1] | Human Data | | | | Animal Data | | |
|---|---|---|---|---|---|---|---|
| | NOEL-CNIH (induction) µg/cm² | NOEL-HMT (induction) µg/cm² | LOEL[2] (induction) µg/cm² | WoE NESIL[3] µg/cm² | LLNA[4] Weighted Mean EC3 Value µg/cm² | GPMT[5] | Buehler[5] |
| Human potency category unknown; Current exposure level below the DST for non-reactive materials. | 16071 | N/A | N/A | N/A | N/A | N/A | Negative |
| | *In vitro* Data[6] | | | | *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 | Michael addition | No alert found |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; 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]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
[5]Studies conducted according to the OECD TG 406 are included in the table..
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table..

of concern for photoirritating or photoallergenic effects, 1000 L $mol^{-1}$ • $cm^{-1}$ (Henry et al., 2009).

**Additional References:** RIFM, 1980d.

**Literature Search and Risk Assessment Completed On:** 08/22/23.

### 11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene 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 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene. Based on the Creme RIFM Model, the inhalation exposure is 0.0015 mg/day. This exposure is 313.3 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:** 08/22/23.

## 11.2. Environmental Endpoint Summary

### 11.2.1. Screening-level Assessment

A screening-level risk assessment of 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene 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, 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene 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).

*11.2.1.1. Risk Assessment.* Based on the current VoU (2019), 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo [2.2.1]hept-2-ene presents no risk to the aquatic compartment in the screening-level assessment.

*11.2.1.2. Key Studies.* ***Biodegradation***:
No data available.
***Ecotoxicity***:
No data available.

*11.2.1.3. Other available data.* 2-Propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene has been pre-registered for REACH with no additional data at this time.

*11.2.1.4. 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.

**Table 2**
Supported concentrations for 2-propanol, reaction products with boron trifluoride and 5-ethylidenebicyclo[2.2.1]hept-2-ene that present no appreciable risk for skin sensitization based on non-reactive DST.

| IFRA Category[a] | Description of Product Type | Supported Concentrations[b] (%) 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[c] |
| 2 | Products applied to the axillae | 0.021 | $4.1 \times 10^{-5}$ |
| 3 | Products applied to the face using fingertips | 0.41 | NRU[c] |
| 4 | Fine fragrance products | 0.39 | NRU[c] |
| 5 | Products applied to the face and body using the hands (palms), primarily leave-on | 0.10 | NRU[c] |
| 6 | Products with oral and lip exposure | 0.23 | NRU[c] |
| 7 | Products applied to the hair with some hand contact | 0.79 | NRU[c] |
| 8 | Products with significant ano-genital exposure | 0.041 | No Data[d] |
| 9 | Products with body and hand exposure, primarily rinse-off | 0.75 | $2.7 \times 10^{-5}$ |
| 10 | Household care products with mostly hand contact | 2.7 | 0.052 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate | 1.5 | No Data[d] |
| 12 | Products not intended for direct skin contact, minimal or insignificant transfer to skin | No Restriction | NRU[c] |

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent maximum acceptable concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] No reported use.
[d] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Exposure information and PEC calculation (following RIFM

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>15.05</u> | | | 1000000 | 0.01505 | |

Environmental Framework: Salvito et al., 2002).

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ Used | 3.55 | 3.55 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional VoU Tonnage Band | <1 | Not reported |
| **Risk Characterization: PEC/PNEC** | **<1** | **N/A** |

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

The RIFM PNEC is 0.01505 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 08/18/23.

## 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 03/18/24.

## 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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