Short review

RIFM fragrance ingredient safety assessment, elemol, CAS Registry Number 639-99-6

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Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how

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exposure to biological systems and the environment. The repeated dose, developmental and reproductive endpoints were completed using the TTC (Threshold of Toxicological Concern) for Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

### RIFM's Expert Panel*

*This results in the following endpoints:

**PBT** - Persistent, Bioaccumulative, and Toxic  
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration  
**QRA** - Quantitative risk assessment  
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals  
**RIFM** - Research Institute for Fragrance Materials  
**RQ** - Risk Quotient  
**TTC** - Threshold of Toxicological Concern  
**UV/Vis Spectra** - Ultra Violet/Visible spectra  
**VCF** - Volatile Compounds in Food  
**VoU** - Volume of Use  
**vPvB** - (very) Persistent, (very) Bioaccumulative  
**WOE** - Weight of Evidence

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### 1. Identification

1. **Chemical Name**: Elemol  
2. **CAS Registry Number**: 639-99-6  
3. **Synonyms**: Cyclohexanemethanol, 4-ethenyl-α,γ,4-trimethyl-3-(1-methylthienyl)-, [1R-(1alpha,3alpha,4beta; (15S,25R)-(-)-α,α-Dimethyl-1-vinyl-o-meth-8-ene-4-methanol; Elemol; α-Elemol; 2-(3-イソプロピルヘキシル-4-ピニル-4-メチルシクロヘキシル)プロパン-2-オール; 2-(3-Isopropenyl-4-methyl-4-vinylcyclohexyl)propan-2-ol  
4. **Molecular Formula**: C15H26O  
5. **Molecular Weight**: 222.37  
6. **RIFM Number**: 6263

### 2. Physical data

1. **Boiling Point**: 275 °C (EPI Suite)  
2. **Flash Point**: 210.00 °F (TCC (98.89 °C)*  
3. **Log Kow**: 5.54 (EPI Suite), 2.5 and 4.4 (RIFM, 2011)  
4. **Melting Point**: 50.56 °C (EPI Suite)  
5. **Water Solubility**: 1.99 mg/L (EPI Suite)  
6. **Specific Gravity**: Not Available  
7. **Vapor Pressure**: 0.000193 mm Hg @ 20 °C (EPI Suite 4.0), 0.005 mm Hg 20C [FMA database], 0.000385 mm Hg @ 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\(^{-1}\))

### 3. Exposure

1. **Volume of Use (worldwide band)**: 1–10 metric tons per year (IFRA, 2011)  
2. **Average Maximum Concentration in Hydroalcohols**: 0.07% (IFRA, 2004)  
3. **97.5th Percentile**: 0.05% (IFRA, 2004)  
4. **Dermal Exposure**: 0.0013 mg/kg/day (IFRA, 2004)
5. Computational toxicology evaluation

6. Metabolism

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

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5 Oral Exposure: Not applicable
6 Inhalation Exposures**: 0.000077 mg/kg/day or 0.0046 mg/day [IFRA, 2004]
7 Total Systemic Exposure (Dermal + Inhalation): 0.0014 mg/kg/day

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

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

4. Derivation of systemic absorption

1 Dermal: Assumed 100%
2 Oral: Data not available - not considered.
3 Inhalation: Assumed 100%
4 Total: Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.0014 mg/kg/day

5. Computational toxicology evaluation

1 Cramer Classification: Class I, Low (Expert Judgment)

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree v 2.6</th>
<th>OECD QSAR Toolbox v 3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>I*</td>
<td>I</td>
<td>III</td>
</tr>
</tbody>
</table>

*See Appendix below for explanation.

2 Analogues Selected:
   a Genotoxicity: None
   b Repeated Dose Toxicity: None
   c Developmental and Reproductive Toxicity: None
   d Skin Sensitization: None
   e Phototoxicity/Photallergenicity: None
   f Local Respiratory Toxicity: None
   g Environmental Toxicity: None
3 Read-across Justification: None

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

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


8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 10/31/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Elemol was assessed in the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity indicating a lack of genotoxic potential (RIFM, 2013). The mutagenic activity of elemol was assessed in a GLP compliant Ames assay conducted in accordance with OECD TG 471. Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli tester strains WP2 uvrA were treated with elemol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No significant increases in the number of revertant colonies was observed (RIFM, 2014a). Under the conditions of the study, elemol was considered not mutagenic in bacteria.

The clastogenic activity of elemol was assessed in an in vitro micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with elemol in DMSO up to concentrations of 220 μg/ml in the presence and absence of metabolic activation. The test material did not induce any significant increases in the percentage of cells with micronucleated binucleated cells relative to vehicle control at any dose level (RIFM, 2014b). Under the conditions of the assay, elemol was concluded to be negative for the induction of micronuclei in the non-activated and S9-activated test systems in the in vitro mammalian micronucleus test using human peripheral blood lymphocytes.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/15/2013

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on elemol or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data...
on elemol or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure for elemol (1.4 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint.

Additional References: Bhatia et al., 2008; Belsito et al., 2008.


10.1.3. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on elemol or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on elemol or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure for elemol (1.4 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental or reproductive toxicity endpoints.

Additional References: Bhatia et al., 2008; Belsito et al., 2008.


10.1.4. Skin sensitization

Based on the application of the non-reactive DST, elemol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the application of the non-reactive DST, elemol does not present a significant concern for skin sensitization. There are no data available or suitable read across identified for elemol. Elemol is predicted to be non-reactive to skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). The current reported exposure of elemol was evaluated against the non-reactive DST. The current dermal exposure from hydroalcoholic products, 0.07%, is below the DST for non-reactive materials when evaluated in QRA categories 3 and 4 (DST levels of 0.14% and 0.41%, respectively).

Additional References: None.


10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, elemol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for elemol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern (1000 L mol⁻¹ cm⁻¹) for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, elemol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.


10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on elemol. Based on the IFRA survey results for hydroalcohols, the 97.5th percentile was reported to be 0.05%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.0046 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 304.3 times lower than the Cramer Class I TTC value of 1.4 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.


10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

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

A screening-level hazard assessment using EPISUITE ver 4.1 did identify elemol as being possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

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

10.2.3. Key studies

10.2.3.1. Biodegradation. Not data available.

10.2.3.2. Ecotoxicity. RIFM, 2005: A 10 day short term toxicity test with Daphnia magna were conducted according to the EPA/600/4-90/027 and ASTM E729 method. The calculated LC50 was reported to be 4.74 mg/l. The 10 day NOECs were 0.75 mg/l and 2.99 mg/l for reproduction and survival, respectively.

RIFM, 2005: Short-term chronic static renewal effluent toxicity
test with immature fathead minnows, *Pimephales promelas* was conducted according to the EPA/600/4–90/027 and ASTM E729 method. The 7-day LC50 of elemol in fathead minnow fry (*Pimephales promelas*) exceeded 5.97 mg/l with NOEC of 2.99 mg/l for survival and growth.

### 10.2.3.3. Other available data
Elemol has been pre-registered for REACH with no additional data at this time.

### 11. Risk assessment refinement

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

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

Endpoints used to calculate PNEC are underlined.

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>RIFM Framework Screening Level (Tier 1)</th>
<th>ECOSAR Acute Endpoints (Tier 2) Ver.1.11</th>
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</thead>
<tbody>
<tr>
<td>Neutral Organics</td>
<td>2.44 mg/L</td>
<td>1.277 mg/L</td>
</tr>
<tr>
<td></td>
<td>1,000,000</td>
<td>0.905 mg/L</td>
</tr>
<tr>
<td></td>
<td>0.00244 μg/L</td>
<td>1.685 mg/L</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td>0.0905 μg/L</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
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<th>Exposure</th>
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<th>North America (NA)</th>
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<tr>
<td>Log Kow used</td>
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<td>4.4</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
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<td>1</td>
</tr>
<tr>
<td>Dilution Factor</td>
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<td>3</td>
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<tr>
<td>Regional Volume of Use Tonnage Band</td>
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<tr>
<td>Risk Characterization: PEC/PNEC</td>
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<td>&lt;1</td>
</tr>
</tbody>
</table>

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

The RIFM PNEC is 0.0905 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed on:** 11/15/2013

### 12. Literature search*
- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **OECD Toolbox**
- **SciFinder:** [https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf](https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf)
- **IARC:** [http://monographs.iarc.fr](http://monographs.iarc.fr)
- **OECD SIDS:** [http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html](http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html)
- **EPA Actor:** [http://actor.epa.gov/actor/faces/ACToRHome.jsp?jsessionid=0EF5C212B7906229F477472A9A4D05B7](http://actor.epa.gov/actor/faces/ACToRHome.jsp?jsessionid=0EF5C212B7906229F477472A9A4D05B7)
- **US EPA HPVIS:** [http://www.epa.gov/hpv/hpvis/index.html](http://www.epa.gov/hpv/hpvis/index.html)
- **US EPA Robust Summary:** [http://cfpub.epa.gov/hpv-s/](http://cfpub.epa.gov/hpv-s/)
- **Google:** [https://www.google.com/webhp?tab%3dww%26ei%3dKMSoUpiQK-arsQ5Qs324GwB8g%26ved%3d0CBQQ1S4](https://www.google.com/webhp?tab%3dww%26ei%3dKMSoUpiQK-arsQ5Qs324GwB8g%26ved%3d0CBQQ1S4)

*Information sources outside of RIFM’s database are noted as appropriate in the safety assessment.
This is not an exhaustive list.

**Transparency document**

Transparency document related to this article can be found online at [http://dx.doi.org/10.1016/j.fct.2016.11.027](http://dx.doi.org/10.1016/j.fct.2016.11.027).

**Appendix**

**Explanation of Cramer Classification:** Due to potential discrepancies with the current in silico tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1976).

Q1. Normal constituent of the body? **No.**
Q2. Contains functional groups associated with enhanced toxicity? **No.**
Q3. Contains elements other than C,H,O,N, divalent S? **No.**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No.**

Q16. Common terpene? (see Cramer et al., 1976 for detailed explanation) Yes Class I.

References


