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# Food and Chemical Toxicology

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## Short Review

### RIFM fragrance ingredient safety assessment, diethyl tartrate, CAS Registry Number 87-91-2



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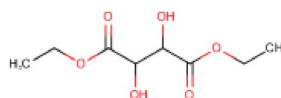
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Version: 121118. This version replaces any previous versions.

Name: Diethyl tartrate CAS Registry Number: 87-91-2



#### 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

**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; Safford et al., 2017) compared to a deterministic aggregate approach

**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts

**DST** - Dermal Sensitization Threshold

**ECHA** - European Chemicals Agency

**EU** - Europe/European Union

**GLP** - Good Laboratory Practice

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IFRA - The International Fragrance Association  
 LOEL - Lowest Observable Effect Level  
 MOE - Margin of Exposure  
 MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition  
 NA - North America  
 NESIL - No Expected Sensitization Induction Level  
 NOAEC - No Observed Adverse Effect Concentration  
 NOAEL - No Observed Adverse Effect Level  
 NOEC - No Observed Effect Concentration  
 NOEL - No Observed Effect Level  
 OECD - Organisation for Economic Co-operation and Development  
 OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines  
 PBT - Persistent, Bioaccumulative, and Toxic  
 PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration  
 QRA - Quantitative Risk Assessment  
 REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals  
 RfD - Reference Dose  
 RIFM - Research Institute for Fragrance Materials  
 RQ - Risk Quotient  
**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 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.**

Diethyl tartrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that diethyl tartrate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to diethyl tartrate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data show that there are no safety concerns for diethyl tartrate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; diethyl tartrate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; diethyl tartrate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are  $< 1$ .

#### Human Health Safety Assessment

**Genotoxicity:** Not genotoxic.

(RIFM, 2017c; 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:** Not a sensitization concern under the current, declared levels of use.

ECHA REACH Dossier: Diethyl Tartrate; ECHA (2016)

**Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic.

(UV Spectra, RIFM Database)

**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

#### Environmental Safety Assessment

**Hazard Assessment:**

**Persistence:**

Critical Measured Value: 85% (OECD 301D)

(ECHA REACH Dossier: Diethyl Tartrate; ECHA, 2016)

**Bioaccumulation:**

Screening-level: 3.162 L/kg

(EPI Suite v4.11; US EPA, 2012a)

**Ecotoxicity:**

Screening-level: Fish LC50: 17941 mg/L

(RIFM Framework; Salvito et al., 2002)

**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**

Screening-level: PEC/PNEC (North America and Europe)  $< 1$

(RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 17941 mg/L

(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 17.942  $\mu\text{g/L}$

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level

## 1. Identification

- 1. Chemical Name:** Diethyl tartrate
- 2. CAS Registry Number:** 87-91-2
- 3. Synonyms:** Butanedioic acid, 2,3-dihydroxy-[R-(R\*,R\*)]-, diethyl ester; Diethyl 2,3-dihydroxysuccinate; Diethyl 2,3-dihydroxybutanedioate; Ethyl tartrate; Diethyl tartarate; Diethyl tartrate
- 4. Molecular Formula:**  $\text{C}_8\text{H}_{14}\text{O}_6$
- 5. Molecular Weight:** 206.19
- 6. RIFM Number:** 6888

**7. Stereochemistry:** R-(R\*,R\*) isomer specified. Two chiral centers present and 4 total stereoisomers possible.

## 2. Physical data

- 1. Boiling Point:** 288.14 °C (EPI Suite)
- 2. Flash Point:**  $> 200$  °F; CC (FMA Database),  $> 93$  °C (GHS)
- 3. Log  $K_{OW}$ :**  $-0.08$  (EPI Suite)
- 4. Melting Point:** 3.82 °C (EPI Suite)
- 5. Water Solubility:** 71920 mg/L (EPI Suite)

6. **Specific Gravity:** 1.20 (FMA Database)
7. **Vapor Pressure:** 0.000138 mm Hg @ 20 °C (EPI Suite v4.0), 0.000259 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<sup>-1</sup> · cm<sup>-1</sup>)
9. **Appearance/Organoleptic:** A colorless viscous liquid with a very faint winery odor

### 3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.014% (RIFM, 2017a)
3. **Inhalation Exposure\*:** 0.000028 mg/kg/day or 0.0021 mg/day (RIFM, 2017a)
4. **Total Systemic Exposure\*\*:** 0.00075 mg/kg/day (RIFM, 2017a)

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

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

### 4. Derivation of systemic absorption

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

### 5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

#### 2. Analogs Selected:

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

### 6. Metabolism

No relevant data available for inclusion in this safety assessment.

### 6.1. Natural occurrence (discrete chemical) or composition (NCS)

Diethyl tartrate is reported to occur in the following foods by the VCF\*:

- Sherry.
- 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.

### 7. IFRA standard

None.

### 8. REACH dossier

Available; accessed 10/09/18.

### 9. Summary

#### 9.1. Human Health Endpoint Summaries

##### 9.1.1. Genotoxicity

Based on the current existing data, diethyl tartrate does not present a concern for genotoxicity.

**9.1.1.1. Risk assessment.** Diethyl tartrate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of diethyl tartrate 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 diethyl tartrate in water 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, 2017c). Under the conditions of the study, diethyl tartrate was not mutagenic in the Ames test.

The clastogenic activity of diethyl tartrate 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 diethyl tartrate in water at concentrations up to 2000 µg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Diethyl tartrate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, diethyl tartrate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/08/18.

### 9.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on diethyl tartrate or any read-across materials. The total systemic exposure to diethyl tartrate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**9.1.2.1. Risk assessment.** There are no repeated dose toxicity data on diethyl tartrate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to diethyl tartrate (0.75 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/16/18.

### 9.1.3. Reproductive toxicity

There are no reproductive toxicity data on diethyl tartrate or on any read-across materials. The total systemic exposure to diethyl tartrate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**9.1.3.1. Risk assessment.** There are no reproductive toxicity data on diethyl tartrate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to diethyl tartrate (0.75 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/16/18.

### 9.1.4. Skin sensitization

Based on the existing data, diethyl tartrate does not present a safety concern for skin sensitization under the current, declared levels of use.

**9.1.4.1. Risk assessment.** Based on the existing data, diethyl tartrate is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay, diethyl tartrate was found to be non-sensitizing up to 100% (<https://echa.europa.eu/registration-dossier/-/registered-dossier/18416/7/5/2> ECHA, 2016).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, diethyl tartrate does not present a concern for skin sensitization under the current, declared levels of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/07/18.

### 9.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, diethyl tartrate would not be expected to present a concern for phototoxicity or photoallergenicity.

**9.1.5.1. Risk assessment.** There are no phototoxicity studies available for diethyl tartrate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, diethyl tartrate does not present a concern for phototoxicity or photoallergenicity.

**9.1.5.2. 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<sup>-1</sup> · cm<sup>-1</sup> (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/18/18.

### 9.1.6. Local Respiratory Toxicity

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

**9.1.6.1. Risk assessment.** There are no inhalation data available on diethyl tartrate. Based on the Creme RIFM Model, the inhalation exposure is 0.0021 mg/day. This exposure is 667 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.

**Literature Search and Risk Assessment Completed On:** 11/13/18.

## 9.2. Environmental endpoint summary

### 9.2.1. Screening-level assessment

A screening-level risk assessment of diethyl tartrate 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<sub>OW</sub>, 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, diethyl tartrate 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 ECHA, 2012a) did not identify diethyl tartrate 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 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, 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 ≥ 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 BOWIN 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.

### 9.2.2. Risk assessment

Based on the current Volume of Use (2015), diethyl tartrate presents no risk to the aquatic compartment in the screening-level assessment.

#### 9.2.2.1. Key studies

9.2.2.1.1. *Biodegradation*. No data available.

9.2.2.1.2. *Ecotoxicity*. No data available.

9.2.2.1.3. *Other available data*. Diethyl tartrate has been registered under REACH and the following additional data is available:

A ready biodegradability (closed bottle test) study was conducted according to the OECD 301D method, and biodegradation of 85% was observed after 28 days.

An algae growth inhibition study was conducted according to the OECD 201 method, and the 72-h EC50 (growth rate) was reported to be 169.44 mg/L (ECHA, 2016).

#### 9.2.3. Risk assessment refinement

Since diethyl tartarate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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)	<u>17941</u>			1000000	17.942	

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

Exposure	Europe (EU)	North America (NA)
Log K <sub>ow</sub> Used	-0.08	-0.08
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt; 1</b>	<b>&lt; 1</b>

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

The RIFM PNEC is 17.942 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level 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: 11/16/18.**

## 10. 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**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <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/oppphpv/public\\_search\\_publicdetails?submission\\_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User\\_title=DetailQuery%20Results&EndPointRpt=Y#submission](https://ofmpub.epa.gov/oppphpv/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](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](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)
- **Google:** <https://www.google.com>
- **ChemIDplus:** <https://chem.nlm.nih.gov/chemidplus/>

Search keywords: CAS number and/or material names.

\*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

## 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.

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