Food and Chemical Toxicology 115 (2018) S114–S123

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

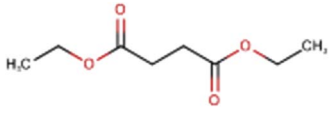
Short review

RIFM fragrance ingredient safety assessment diethyl succinate, CAS Registry Number 123-25-1

A.M. Api[a,*], D. Belsito[b], D. Botelho[a], D. Browne[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], R. Parakhia[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], Y. Thakkar[a], E.H. Theophilus[a], A.K. Tiethof[a], Y. Tokura[m], S. Tsang[a], J. Wahler[a]

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

Version: 102417. This version replaces any previous versions.
Name: Diethyl succinate
CAS Registry Number: 123-25-1



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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach

* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

https://doi.org/10.1016/j.fct.2017.12.050
Received 30 October 2017; Received in revised form 20 December 2017; Accepted 22 December 2017
Available online 28 December 2017

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
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
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
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Significant - statistically significant difference in reported results as compared to controls with a $p < .05$ using appropriate statistical test.
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

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

Diethyl succinate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read across analog dimethyl succinate (CAS # 106-65-0) show that diethyl succinate is not expected to be genotoxic and there are no safety concerns for skin sensitization under the current, declared levels of use. The repeated dose and local respiratory toxicity endpoints were completed using pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) as a read across analog, which provided a MOE > 100. The reproductive toxicity endpoint was completed using pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) and dibasic ester (DBE) mix (CAS # 95481-62-2) as read across analogs, which provided a calculated MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; diethyl succinate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, diethyl succinate 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.	(ECHA REACH Dossier: dimethyl succinate; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 7.5 mg/kg/day.	(ECHA REACH Dossier: dimethyl glutarate)
Reproductive Toxicity: Developmental: NOAEL = 20.5 mg/kg/day Fertility: NOAEL = 129.5 mg/kg/day.	(ECHA REACH Dossier: dimethyl glutarate; Kelly, 1998)
Skin Sensitization: Not a sensitization concern.	(ECHA REACH Dossier: dimethyl succinate)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOEC = 50 mg/m^3.	(ECHA REACH Dossier: dimethyl glutarate)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-Level: 2.87 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening-Level: 3.09 L/kg (US EPA, 2012a)
Ecotoxicity: Screening-Level: Fish LC50: 797.5 mg/L (RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 797.5 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.7975 µg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Diethyl succinate
2. **CAS Registry Number:** 123-25-1
3. **Synonyms:** Butanedioic acid, diethyl ester; Diethyl butanedioate; Diethyl ethanedicarboxylate; Ethyl succinate; Morflex Diethyl Succinate; Succinic acid, diethyl ester; ｺﾊｸ酸ｼﾞｱﾙｷﾙ(C = 1 ~ 18); Diethyl succinate
4. **Molecular Formula:** $C_8H_{14}O_4$
5. **Molecular Weight:** 174.2
6. **RIFM Number:** 663

2. Physical data

1. **Boiling Point:** 218 °C [FMA Database], 186.96 °C [US EPA, 2012a]
2. **Flash Point:** 91 °C [GHS Database], 195 °F; CC [FMA Database]
3. **Log K_{OW}:** 1.39 [US EPA, 2012a]
4. **Melting Point:** −71.54 °C [US EPA, 2012a]
5. **Water Solubility:** 5547 mg/L [US EPA, 2012a]
6. **Specific Gravity:** 1.035–1.040 [FMA Database], 1.037–1.042 [FMA Database]
7. **Vapor Pressure:** 0.0975 mmHg @ 20 °C [US EPA, 2012a], 0.08 mm Hg 20C [FMA Database], 0.147 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A clear, colorless to pale yellow liquid having a faint, pleasant odor remotely winey-ethereal.

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 1.08% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000032 mg/kg/day or 0.0022 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.027 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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, 2017; 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
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2. Analogs Selected:
   a. **Genotoxicity:** Dimethyl succinate (CAS # 106-65-0)
   b. **Repeated Dose Toxicity:** Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0)
   c. **Reproductive Toxicity:** Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) and dibasic ester (DBE) mix (CAS # 95481-62-2)
   d. **Skin Sensitization:** Dimethyl succinate (CAS # 106-65-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0)
   g. **Environmental Toxicity:** None
3. Read across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Diethyl succinate is reported to occur in the following foods*:

Anise brandy
Apple brandy (Calvados)
Apple processed (*Malus* species)
Arctic bramble (*Rubus arcticus* l.)
Arrack
Artocarpus species
Bantu beer
Beef
Beer
Bilberry wine
Cherry brandy
Chinese quince (Pseudocydonia sinensis schneid)
Cider (apple wine)

Citrus fruits
Cocoa category
Date (*Phoenix dactylifera* l.)
Elderberry (*Sambucus nigra* l.)
Grape (*Vitis* species)
Grape brandy
Guava wine
Honey
Litchi wine
Mangifera species
Mulberry spirit (mouro)
Passion fruit (*Passiflora* species)
Pear brandy
Pineapple (*Ananas comosus*)
Plum brandy
Pomegranate wine (*Punica granatum* l.)
Prickly pear (*Opuntia ficus* indica)
Raspberry brandy
Raspberry, blackberry and boysenberry
Rum
Sake
Sherry
Shoyu (fermented soya hydrolysate)
Starfruit (*Averrhoa carambola* l.)
Strawberry wine
Tequila (*Agave* tequilana)
Vinegar
Whisky
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 that contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 10/19/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Diethyl succinate was assessed in the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of diethyl succinate; however, read across can be made to dimethyl succinate (CAS # 106-65-0; see Section V). The mutagenic activity of dimethyl succinate 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 TA97A, TA98, TA100, TA102, and TA1535 were treated with dimethyl succinate in water at concentrations up to 5000 μg/plate. No increase in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier on Dimethyl succinate). Under the conditions of the study, dimethyl succinate was not mutagenic in the Ames test, and this can be extended to diethyl succinate.

There are no studies assessing the clastogenic activity of diethyl succinate; however, read across can be made to dimethyl succinate (CAS # 106-65-0; see Section V). The clastogenic activity of dimethyl succinate 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 dimethyl succinate in DMSO (dimethyl sulfoxide) at concentrations up to 2260 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Dimethyl succinate did not induce binucleated cells with micronuclei when tested up to cytotoxic level in either non-activated or S9-activated test systems (RIFM, 2015). Under the conditions of the study, dimethyl succinate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to diethyl succinate.

Based on the data available, dimethyl succinate does not present a concern for genotoxic potential, and this can be extended to diethyl succinate.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/16/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for diethyl succinate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on diethyl succinate. Read across material, pentanedioic acid, 1,5-dimethyl ester (dimethyl glutarate) (CAS # 1119-40-0; see Section V), has sufficient repeated dose toxicity data. In a GLP-compliant study, Sprague-Dawley rats (36/sex/dose) were exposed to dimethyl glutarate (DMG) via inhalation (whole body) at 0, 10, 50 or 400 mg/m3 (0, 0.01, 0.05 or 0.4 mg/L), 6 h/day, 5 days/week for 90 days. The exposure period was followed by a 1-month recovery period. Compound-related effects were observed in the noses of male and female rats exposed to 400 mg/m^3 of DMG for 90 days. The lesions were usually focal and minimal in severity. According to the ECHA CoRAP conclusions, the main observation of degeneration/atrophy of the olfactory mucosa is considered as species dependent and not relevant to humans. In male rats exposed to pentanedioic acid, 1,5-dimethyl ester, serum testosterone concentrations were statistically significantly decreased at concentrations of 50 and 400 mg/m^3 (59 and 50% of control, respectively). Similarly, serum LH concentrations were decreased in a dose-dependent manner and were statistically significantly decreased at 400 mg/m^3 (71% of control). Serum concentrations of FSH were not affected by pentanedioic acid, 1,5-dimethyl ester treatment. In female rats, pentanedioic acid, 1,5-dimethyl ester exposure did not alter serum estradiol or progesterone concentrations. There was a treatment-related increase in epididymal sperm counts (per cauda epididymis and per gram cauda epididymis) following exposure to pentanedioic acid, 1,5-dimethyl ester and the number of sperm per cauda and per gram cauda epididymis was significantly increased at 50 and 400 mg/m^3 (124–131% of control). Also, the increased sperm count may be considered to be not adverse as it does not represent functional impairment in the test organism. Under the conditions of this study, the repeated dose toxicity NOAEC may be considered to be 50 mg/m^3 (0.05 mg/L), based on statistically significantly lower mean body weights and mean body weight gains among high-dose males during the study and statistically significantly lower food consumption among high-dose males and females. Using standard minute volume and body weight values for male Sprague-Dawley rats, the calculated NOAEL for repeated dose toxicity is 13 mg/kg/day (ECHA REACH Dossier: dimethyl glutarate, accessed on 3/14/2017). Since the dimethyl glutarate is a volatile chemical, a 50% retention factor was

conservatively considered to derive a systemic dose (the application of a 50% retention factor was approved by the Expert Panel for Fragrance Safety*). Thus, the refined NOAEL for the repeated dose toxicity was considered to be 7.5 mg/kg/day. **Therefore, the diethyl succinate MOE for the repeated dose toxicity endpoint can be calculated by dividing the dimethyl glutarate NOAEL in mg/kg/day by the total systemic exposure to diethyl succinate, 7.5/0.027 or 278.**

*The Expert Panel for fragrance safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed on: 3/22/2017.

10.1.3. Reproductive toxicity

The margin of exposure for diethyl succinate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on diethyl succinate. Read across material, pentanedioic acid, 1,5-dimethyl ester (dimethyl glutarate or DMG) (CAS # 1119-40-0; see Section V), has sufficient developmental toxicity data. In a GLP-compliant study, time-mated New Zealand White rabbits (22/dose) were exposed via inhalation (whole body, 6 h/day) to DMG concentrations of 0, 30, 100, 300 or 1000 mg/m^3 (0.03, 0.1, 0.3 or 1.0 mg/L) during gestation. Treatment-related signs of toxicity (ocular discharge – likely due to eye irritation) and significant reductions in body weight gain were seen at 300 mg/m^3 and above. Two mortalities (one doe found dead and one euthanized in extremis) were observed in the highest dose group. There were no compound-related effects at any level on embryofetal viability or on fetal sex ratio, fetal body weight, fetal malformations or fetal variations. A marked increase in delayed ossification was observed at 1000 mg/m^3. Using standard minute volume and body weight values for female New Zealand rabbits, the calculated NOAEL for developmental toxicity is considered to be 41 mg/kg/day, respectively (ECHA REACH dossier: dimethyl glutarate). Since the dimethyl glutarate is a volatile chemical, a 50% retention factor was conservatively considered to derive a systemic dose (the application of a 50% retention factor was approved by the Expert Panel for Fragrance Safety*). Thus, the refined NOAEL for the repeated dose toxicity was considered to be 20.5 mg/kg/day. **Therefore, the diethyl succinate MOE for the developmental toxicity endpoint can be calculated by dividing the dimethyl glutarate NOAEL in mg/kg/day by the total systemic exposure to diethyl succinate, 20.5/0.027 or 759.**

There are limited reproductive toxicity data on diethyl succinate. Read across material, dibasic ester (DBE) mix (CAS # 95481-62-2; see Section V) has sufficient reproductive dose toxicity data. DBE is a mixture of 10–25% DMA (dimethyl adipate CAS # 627-93-0), 55–65% DMG (dimethyl glutarate CAS # 1119-40-0) and 15–25% DMS (dimethyl succinate CAS # 106-65-0). In a GLP-compliant inhalation reproductive toxicity study, groups of Crl:CD®(SD)BR rats (20/sex/dose) were mated after exposure for six hours a day, five days a week, for about 14 weeks to DBE vapor concentrations of 160 or 400 mg/m^3 (maximum attainable vapor), or to 1000 mg/m^3 (aerosol) of a DBE mixture. DBE exposure continued during breeding (15 days), gestation (21 days), and lactation (21 days) periods. DBE exposures were discontinued for the dams after the 19th gestation day and begun again on day four postpartum. Offspring were not subjected to DBE exposure. It is concluded that reproduction in rats was not altered by repeated inhalation exposure to up to 1.0 mg/L DBE, a concentration that produced both body weight and histologic effects in parental rats. The fertility NOAEC was 1000 mg/m^3 (1.0 mg/L). Using standard minute volume and body weight values for male and female Sprague-Dawley rats, the calculated NOAEL for fertility toxicity is 259 mg/kg/day (Kelly, 1998). Since the dibasic ester is a volatile chemical, a 50% retention factor was conservatively considered to derive a systemic dose (the application of a 50% retention factor was approved by the Expert Panel for Fragrance Safety*). Thus, the refined NOAEL for the repeated dose toxicity was considered to be 129.5 mg/kg/day. **Therefore, the diethyl succinate MOE for the fertility toxicity endpoint can be calculated by dividing the dibasic ether NOAEL in mg/kg/day by the total systemic exposure to diethyl succinate, 129.5/0.027 or 4796.**

*The Expert Panel for fragrance safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed on: 3/22/2017.

10.1.4. Skin sensitization

Based on the existing data and read across analog dimethyl succinate (CAS # 106-65-0), diethyl succinate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for diethyl succinate. Based on the existing data and read across analog dimethyl succinate (CAS # 106-65-0; see Section V), diethyl succinate does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read across material dimethyl succinate was found to be non-sensitizing up to 100% (ECHA REACH Dossier: dimethyl succinate). Furthermore, in a confirmatory human maximization (HMAX) test, no skin sensitization reactions were observed (RIFM, 1977). In addition, no skin sensitization reactions were observed with diethyl succinate in a confirmatory HMAX test (RIFM, 1975). Based on weight of evidence from structural analysis, human studies, and read across analog dimethyl succinate, diethyl succinate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 3/22/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, diethyl succinate 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 diethyl succinate 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 for phototoxicity and photoallergenicity, 1000 L·mol^{-1}·cm^{-1} (Henry, 2009). Based on lack of absorbance, diethyl succinate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/28/17.

10.1.6. Local respiratory toxicity

There are insufficient inhalation data available on diethyl succinate; however, in 90-day sub-chronic inhalation toxicity study for the analog dimethyl glutarate (CAS # 1119-40-0; see Section V), a NOEC of 50 mg/m^3 is reported (ECHA REACH Dossier: dimethyl glutarate).

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 90-day sub-chronic inhalation toxicity study conducted in rats, a NOEC of 50 mg/m^3 was reported for pentanedioic acid, 1,5-dimethyl ester (dimethyl glutarate) (ECHA Dossier on Dimethyl glutarate). Six groups of male and six groups of female Crl:CD®(SD)IGS BR rats were exposed to 0, 10, 50, or 400 mg/m^3 dimethyl glutarate for 6 h per day, 5 days week. A clinical pathology evaluation, neurobehavioral test battery, and estrous cycle determination were made for all groups. Microscopic test findings indicated test substance-related effects in the nasal passageways of males and females exposed to 400 mg/m^3. Microscopic findings included: degeneration/atrophy of the olfactory mucosa of the dorsal meatus and of the dorsomedial aspect of the dorsal endoturbinate; focal respiratory metaplasia of the olfactory mucosa of the dorsal meatus; and lesions were minimal to mild in severity and occurred in higher incidences in the dimethyl glutarate treated groups. The NOEC for local respiratory toxicity was determined to be 50 mg/m^3, based on the pathology of animals in the 400 mg/m^3 exposure group.

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

- (50.0 mg/m^3) (1m^3/1000L) = 0.050 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.050 mg/L) (61.2 L/d) = 3.06 mg/day
- (3.06 mg/day)/(0.0016 kg lung weight of rat*) = 1912.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0022 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015, 2017; Comiskey, 2017). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.0034 mg/kg lung weight/day resulting in a MOE of 562500 (i.e., [1912.5 mg/kg lung weight/day]/[0.0034 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0022 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: Smyth, 1951.

Literature Search and Risk Assessment Completed on: 3/21/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of diethyl succinate was performed following the RIFM Environmental Framework (Salvito, 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 K_{ow} 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 (US EPA, 2012b; 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, which is considered proprietary information, 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, diethyl succinate 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 diethyl succinate as possibly persistent or 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 EPI Suite v4.11).

10.2.2. Risk assessment

Based on current Volume of Use (2011), diethyl succinate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Diethyl succinate has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	797.5 mg/L			1,000,000	0.7975 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.39	1.39
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.7975 µg/L. The revised PEC/PNECs for EU and NA: Not applicable; 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: 3/20/17.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.12.050.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.050.

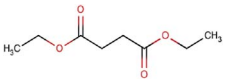
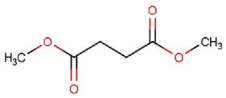
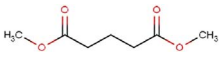
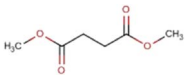
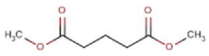
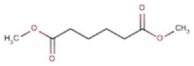
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read across material		
Principal Name	Diethyl succinate	Dimethyl succinate	Pentanedioic acid, 1,5-dimethyl ester	DBE Dibasic Ester
CAS No.	123-25-1	106-65-0	1119-40-0	95481-62-2 (mixture)
Structure				A.  B.  C. 
Similarity (Tanimoto score)		0.92	0.96	A. 0.91 B. 0.96 C. 0.90
Read across endpoint		• Genotoxicity • Skin sensitization	• Repeated dose • Reproductive • Local Respiratory	• Reproductive
Molecular Formula	$C_8H_{14}O_4$	$C_6H_{10}O_4$	$C_7H_{12}O_4$	A. $C_6H_{10}O_4$ B. $C_7H_{12}O_4$ C. $C_8H_{14}O_4$
Molecular Weight	174.20	146.14	160.17	A. 146.14 B. 160.17 C. 174.20
Melting Point (°C, EPISUITE)	−71.54	−95.30	−83.29	A. −95.30 B. −83.29 C. −71.54
Boiling Point (°C, EPISUITE)	186.96	144.16	166.02	A. 196-225 B. 166.02 C. 186.96
Vapor Pressure (Pa @ 25 °C, EPISUITE)	19.7	57.5	23.7	A. 57.5 B. 23.7 C. 91.7
Log Kow (KOWWIN v1.68 in EPISUITE)	1.20	0.35	0.62	A. 0.35 B. 0.62 C. 1.03
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	1910	2500	5900	A. 2500 B. 5900 C. 6000
J_{max} (mg/cm^2/h, SAM)	59.343	38.024	98.151	A. 38.024 B. 98.151 C. 13.907
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	9.77E-007	5.54E-007	7.36E-007	A. 5.54E-007 B. 7.36E-007 C. 9.90E-002
Genotoxicity				
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found		
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found		
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (moderate reliability)		
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found		
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found		
In vivo mutagenicity (Micronucleus) alerts by ISS	• H-acceptor-path 3-H-acceptor	• H-acceptor-path 3-H-acceptor		
Oncologic Classification	• Not classified	• Not classified		

Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Reproductive toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (moderate reliability)		• Non-toxicant (moderate reliability)	
Skin Sensitization				
Protein binding by OASIS v1.4	• No alert found	• No alert found		
Protein binding by OECD	• No alert found	• No alert found		
Protein binding potency	• Not possible to classify	• Not possible to classify		
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found		
Skin Sensitization model (CAESAR) (version 2.1.6)	• Non-sensitizer (moderate reliability)	• Sensitizer (good reliability)		
Respiratory				
Respiratory sensitization OECD QSAR Toolbox (3.4)	• No alert found		• No alert found	
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2	See supplemental data 3	See supplemental data 4

Summary

There are insufficient toxicity data on the target material diethyl succinate (CAS # 123-25-1). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties and expert judgment, dimethyl succinate (CAS # 106-65-0), pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) and DBE dibasic ester (CAS # 95481-62-2) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

- Dimethyl succinate (CAS # 106-65-0) was used as a read across analog for target material diethyl succinate (CAS # 123-25-1) for the genotoxicity and skin sensitization endpoints.
  - ○ The target substance and the read across analog are structurally similar and belong to the structural class of aliphatic diester.
  - ○ The target substance and the read across analog share a carboxylic diester group.
  - ○ The key difference between the target substance and the read across analog is that the target substance is a methyl ester of succinic acid while the read across analog is a methyl ester of a longer chain diacid pentanedionic acid. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoints.
  - ○ Similarity between the target substance and the read across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoints.
  - ○ The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicity endpoints are consistent between the target substance and the read across analog.
  - ○ The target substance and the read across analog are predicted to be H-acceptor-path 3-H-acceptors by the ISS model for in vivo mutagenicity. The data described in the genotoxicity section show that the read across analog does not pose a concern for genotoxicity. Therefore, this prediction will be superseded by the available data.
  - ○ The read across analog is predicted to be a sensitizer by the CAESAR model for skin sensitization, while the target substance is predicted to be non-sensitizer. This also means that the read across analog is predicted to have higher reactivity and toxicity compared to the target substance. There are no other protein binding alerts for the read across analog. The data described in the skin sensitization section show that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, the prediction will be superseded by the available data.
  - ○ The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) was used as a read across analog for target material diethyl succinate (CAS # 123-25-1) for the local respiratory, repeated dose and reproductive toxicity endpoints.
  - ○ The target substance and the read across analog are structurally similar and belong to the structural class of aliphatic diester.
  - ○ The target substance and the read across analog share a carboxylic diester group.
  - ○ The key difference between the target substance and the read across analog is that the target substance is an ethyl ester of succinic acid while

the read across analog is a methyl ester of longer chain diacid pentanedionic acid. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoints.
  - Similarity between the target substance and the read across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoints.
  - The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read across analog.
  - The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- DBE Dibasic Ester (CAS # 95481-62-2) was used as a read across analog for target material diethyl succinate (CAS # 123-25-1) for the reproductive toxicity endpoint.
  - The target substance and the read across analog are structurally similar and belong to the structural class of aliphatic diester.
  - The target substance and the read across analog share a carboxylic diester group.
  - The key difference between the target substance and the read across analog is that the target substance is an ethyl ester of succinic acid while the read across analog is a mixture of diesters. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoint.
  - The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read across analog.
  - The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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