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Short review

RIFM fragrance ingredient safety assessment Dimethyl succinate, CAS Registry Number 106-65-0

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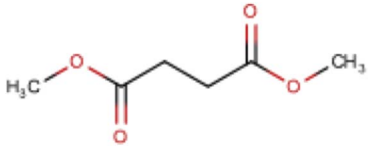
Version: 102017. This version replaces any previous versions.
Name: Dimethyl succinate
CAS Registry Number: 106-65-0



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
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

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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 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 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.
Dimethyl succinate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that dimethyl succinate is not 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 evaluated using pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) as a read across analog, which provided a calculated 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; dimethyl succinate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, dimethyl 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 et al., 1998)
Skin Sensitization: Not sensitizing.	(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: Critical Measured Value: 74.1% (OECD 301B)	(ECHA REACH Dossier: dimethyl glutarate)
Bioaccumulation: Screening-Level: 3.16 L/kg	(RIFM Framework; Salvito et al., 2002)
Ecotoxicity: Screening-Level: Fish LC50: 4861 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: 4861 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 4.861 μg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Dimethyl succinate
2. **CAS Registry Number:** 106-65-0
3. **Synonyms:** Butanedioic acid, dimethyl ester; Dimethyl butanedioate; Methyl butanedioate; Methyl succinate; ｺﾊｸ酸ｼﾞｱﾙｷﾙ(C = 1 ~ 18); Dimethyl succinate
4. **Molecular Formula:** $C_6H_{10}O_4$
5. **Molecular Weight:** 146.14
6. **RIFM Number:** 1013

2. Physical data

1. **Boiling Point:** 200 °C [FMA Database], 144.16 °C [US EPA, 2012a]
2. **Flash Point:** 96 °C [GHS Database], 195 °F; CC [FMA Database]
3. **Log K_{ow}:** 0.4 [US EPA, 2012a]
4. **Melting Point**: −95.3 °C [US EPA, 2012a]
5. **Water Solubility:** 39,620 mg/L [US EPA, 2012a]
6. **Specific Gravity:** 1.117 [FMA Database]
7. **Vapor Pressure:** 0.294 mmHg @ 20 °C [US EPA, 2012a], 0.432 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 · mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Merck Index (1976) A colorless liquid which has a pleasant ethereal-winey, dry-green, slightly fruity odor and a winey, somewhat burning taste.

3. Exposure

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Rinse off Conditioner:** 0.0010% (RIFM, 2016) (No reported use in hydroalcoholics)
3. **Inhalation Exposure*:** 0.00000030 mg/kg/day or 0.000022 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.000057 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 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, 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
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   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:** None
   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)

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

Apple brandy (Calvados)
Filbert, Hazelnut (*Corylus avellano*)
Starfruit (*Averrhoa carambola* L.)

*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

Available, accessed 3/23/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Dimethyl succinate was assessed in the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). 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 increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier: dimethyl succinate). Under the conditions of the study, dimethyl succinate was not mutagenic in the Ames test.

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.

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

Additional References: None.

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

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are limited repeated dose toxicity data on dimethyl succinate. A GLP-compliant subchronic inhalation study was conducted on groups of male and female Sprague-Dawley rats (72/group) exposed via inhalation to 0 or 400 mg/mg^3 dimethyl succinate (DMS) for 6 h a day, 5 days a week over a 90-day period. The exposure period was followed by a 1-month recovery period. The male rats had lower mean body weights and mean body weight gains during the study. In addition, the male and female rats exposed to 400 mg/m^3 DMS had lower food consumption. Compound-related effects were observed in the noses of the male and female rats. In the male rats, epididymal sperm counts (per cauda and per gram cauda epididymis) were significantly increased (153 and 141% of control, respectively). The female rats were reported to have a significant decrease in serum estradiol concentrations. The ECHA CoRAP (ECHA, 2014) evaluation and the TSCA submission (US EPA, 2017) considered the hormonal and sperm effects to be test-material related. However, this was not considered to be adverse. A NOAEL was not established since this was a single dose study (Bamberger et al., 2002). Read across material, pentanedioic acid, 1,5-dimethyl ester (also called dimethyl glutarate) (CAS # 1119-40-0; see Section 5), 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/m^3 (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 the 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 observation of degeneration/atrophy of the olfactory mucosa is considered as species dependent and not relevant to humans. In the male rats exposed to DMG, 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 DMG treatment. In the female rats, DMG exposure did not alter serum estradiol or progesterone concentrations. There was a treatment-related increase in epidydimal sperm counts (per cauda epididymis and per gram cauda epididymis) following exposure to DMG, 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 the high dose males during the study and statistically significantly lower food consumption among the high dose males and females. Using standard minute volume and body weight values for the male Sprague-Dawley rats, the calculated NOAEL for repeated dose toxicity is 13 mg/kg/day. (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 7.5 mg/kg/day. **Therefore, the dimethyl 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 dimethyl succinate, 7.5/0.000057 or 131579.**

In addition, the total systemic exposure to dimethyl succinate (0.057 μg/kg/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.

*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 dimethyl succinate is adequate for the developmental and fertility toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on dimethyl succinate. Read across material, pentanedioic acid, 1,5-dimethyl ester (also called dimethyl glutarate or DMG) (CAS # 1119-40-0; see Section 5), 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 (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 dimethyl succinate MOE for the developmental toxicity endpoint can be calculated by dividing the dibasic ether NOAEL in mg/kg/day by the total systemic exposure to dimethyl succinate, 20.5/0.000057 or 359649.**

There are limited reproductive toxicity data on dimethyl succinate. A GLP-compliant subchronic inhalation study was conducted using

groups of male and female Sprague-Dawley rats (72/group) exposed via inhalation to 0 or 400 mg/mg^3 dimethyl succinate (DMS) for 6 h a day, 5 days a week over a 90-day period. The exposure period was followed by a 1-month recovery period. In female rats, DMS caused a statistically significant decrease in serum estradiol concentrations (43% of control); serum progesterone concentrations were not affected. In the male rats, epididymal sperm counts (per cauda and per gram cauda epididymis) were significantly increased (153 and 141% of control, respectively). The ECHA CoRAP (ECHA, 2014) evaluation and the TSCA submission (US EPA, 2017) considered the hormonal and sperm effects to be test-material related. However, this was not considered to be adverse. A NOAEL was not established since this was a single dose study. The increased sperm count may be considered to be not adverse as it does not represent functional impairment in the test organism. Read across material, dibasic ester (DBE) mix (CAS # 95481-62-2; see Section 5) has sufficient fertility 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 was 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 et al., 1998; #33656). 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 dimethyl 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 dimethyl succinate, 129.5/0.000057 or 2271930.**

In addition, the total systemic exposure to dimethyl succinate (0.057 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

*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, dimethyl succinate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, dimethyl succinate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), dimethyl succinate was found to be non-sensitizing up to 100% (ECHA REACH Dossier: dimethyl succinate). In a confirmatory human maximization test, no skin sensitization reactions were observed (RIFM, 1977). Based on weight of evidence from structural analysis, animal and human studies, dimethyl 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, dimethyl 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 dimethyl 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 et al., 2009). Based on lack of absorbance, dimethyl 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 dimethyl succinate; however, in 90-day sub-chronic inhalation toxicity study for the analog dimethyl glutarate (CAS # 1119-40-0; see Section 5), 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 (also called dimethyl glutarate) (ECHA REACH Dossier: 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 was made for all groups. Microscopic test findings indicated test substance-related effects in the nasal passageways of males and female 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) (1 m^3/1000 L) = 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 0.000022 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015, 2017 and Comiskey et al., 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 et al., 2009) to give 0.000034 mg/kg lung weight/day resulting in a MOE of

56250000 (i.e., [1912.5 mg/kg lung weight/day]/[0.000034 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 0.000022 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: Keenan et al., 1990; Morris et al., 1991; Nair et al., 1996; Bamberger et al., 2002.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of dimethyl succinate 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 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, dimethyl 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 dimethyl 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), dimethyl 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. Dimethyl succinate has been registered under REACH, and the following data is available:

Ready biodegradability of the test material was evaluated according to the OECD 301B method. After 28 days, biodegradation of 74.1% was observed.

Fish (*Danio rerio*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 was reported to be greater than 50 mg/L but less than 100 mg/L.

Daphnia magna immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be greater than 100 mg/L.

Algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based on growth and biomass was reported to be greater than 100 mg/L.

10.2.3. Risk assessment refinement

Since dimethyl succinate 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	4861 mg/L			1,000,000	4.861 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.4	0.4
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 4.861 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=KMSoUpiQK-arsQS324GwBg&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.2017.12.056.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.056.

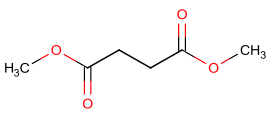
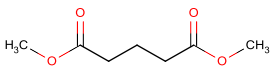
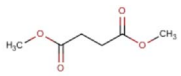
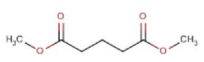
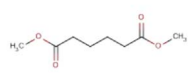
Appendix

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	Dimethyl succinate	Pentanedioic acid, 1,5-dimethyl ester	DBE Dibasic Ester
CAS No.	106-65-0	1119-40-0	95481-62-2
Structure			A.  B.  C. 
Similarity (Tanimoto score)		0.86	A. 1.0 B. 0.96 C. 0.90
Read across endpoint		• Reproductive	• Reproductive

		• Repeated dose • Respiratory	
Molecular Formula	$C_6H_{10}O_4$	$C_7H_{12}O_4$	A. $C_6H_{10}O_4$ B. $C_7H_{12}O_4$ C. $C_8H_{14}O_4$
Molecular Weight	146.14	160.17	A. 146.14 B. 160.17 C. 174.20
Melting Point (°C, EPISUITE)	−95.30	−83.29	A. −95.30 B. −83.29 C. −71.54
Boiling Point (°C, EPISUITE)	144.16	166.02	A. 196-225 B. 166.02 C. 186.96
Vapor Pressure (Pa @ 25 °C, EPISUITE)	57.5	23.7	A. 57.5 B. 23.7 C. 91.7
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	0.35	0.62	A. 0.35 B. 0.62 C. 1.03
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	25,000	59,000	A. 2500 B. 5900 C. 6000
J_{max} (mg/cm^2/h, SAM)	38.024	98.151	A. 38.024 B. 98.151 C. 13.907
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	5.54E-007	7.36E-007	A. 5.54E-007 B. 7.36E-007 C. 9.90E-002
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• No- 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)	
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

Summary

There are insufficient toxicity data on the target material dimethyl succinate (CAS # 106-65-0). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, 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

- Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) was used as a read across analog for target material dimethyl succinate (CAS # 106-65-0) for the local respiratory, reproductive and repeated dose 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 a methyl ester of succinic acid while the read across analog is a methyl ester of the 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 dimethyl succinate (CAS # 106-65-0) 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 a methyl ester of succinic acid while the read across analog is a mixture of C4-C6 diesters. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoint.
  - 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 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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