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Short review

RIFM fragrance ingredient safety assessment, diethyl malonate, CAS Registry Number 105-53-3

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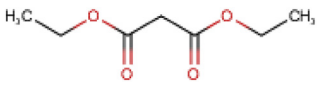
Version: 030818. This version replaces any previous versions.
Name: Diethyl malonate
CAS Registry Number: 105-53-3



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., 2015, 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
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 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 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 use of this material under current conditions is supported by existing information.

The material diethyl malonate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Target data show that diethyl malonate is not genotoxic. The repeated dose and reproductive toxicity endpoints were completed using dimethyl malonate (CAS# 108-59-8) as a read-across analog, which provided an MOE > 100. Data from target material and read-across analog, pentanedioic acid, 1,5-dimethyl ester (CAS# 1119-40-0) show that is material is not a concern for skin sensitization. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; diethyl malonate was found not to be a 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 expected to be genotoxic. (RIFM, 2016b; RIFM, 2016c)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (ECHA Dossier: Dimethyl malonate)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day. (ECHA Dossier: Dimethyl malonate)
Skin Sensitization: No safety concerns under the current, declared levels of use.
(ECHA Dossier: Pentanedioic acid, 1,5-dimethyl ester)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 109% (OECD 301F) (RIFM, 2011)
Bioaccumulation: Screening-level: 3.12 L/kg (EPI Suite; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1956 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: 1956 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.956 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Diethyl malonate
2. **CAS Registry Number:** 105-53-3
3. **Synonyms:** Ethyl malonate; Ethyl methanedicarboxylate; Ethyl propanedioate; Malonic ester; Propanedioic acid, diethyl ester; マロン酸ｱﾙｷﾙ(C = 1 ~ 2)ｴｽﾃﾙ; Diethyl malonate
4. **Molecular Formula:** $C_7H_{12}O_4$
5. **Molecular Weight:** 160.17
6. **RIFM Number:** 715
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 199 °C (FMA), 166.02 °C (EPI Suite)
2. **Flash Point:** 90 °C (GHS), 190 °F
3. **Log K_{OW}:** 0.9 (EPI Suite)
4. **Melting Point**: −83.29 °C (EPI Suite)
5. **Water Solubility:** 10340 mg/L (EPI Suite)
6. **Specific Gravity:** 1.055
7. **Vapor Pressure:** 0.244 mm Hg @ 20 °C (EPI Suite), 0.06 mm Hg 20C (FMA), 0.361 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid which has a sweet, soft and pleasant fruity-green, slightly balsamic odor, reminiscent of apples and has a mild fruity, sweet taste (Merck Index).

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.24% (RIFM, 2016a)
3. **Inhalation Exposure*:** 0.0023 mg/kg/day or 0.17 mg/day (RIFM, 2016a)
4. **Total Systemic Exposure**:** 0.0099 mg/kg/day (RIFM, 2016a)

*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 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; 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**:** Dimethyl malonate (CAS # 108-59-8)
   c. **Reproductive** Toxicity**:** Dimethyl malonate (CAS # 108-59-8)
   d. **Skin Sensitization:** Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0)
   e. **Phototoxicity**/Photoallergenicity**:** None
   f. **Local Respiratory** Toxicity**:** None
   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 malonate is reported to occur in the following foods by the VCF* and is not found in natural complex substances (NCS):

Apple brandy (*Calvados*)	Pineapple (*Ananas comosus*)
Bilberry wine	Raspberry, blackberry, and boysenberry
Cape gooseberry (*Physalis peruviana* L.)	Strawberry wine
Grape (*Vitis* species)	Whisky
Grape Brandy	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.

8. IFRA standard

None.

9. REACH dossier

Dossier available, accessed 09/12/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic activity of diethyl malonate 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 and pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with diethyl malonate in dimethyl sulfoxide (DMSO) 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 in the plate incorporation assay and in the absence of S9 in the pre-incubation method. Small, statistically significant increases in revertant colony frequency were observed in the pre-incubation test at 150 μg/plate (TA100 and TA1535) dosed in the presence of S9-mix only. However, there was no dose-response relationship or reproducibility in the increases observed. Furthermore, the increases were within the vehicle historical control range, hence were considered to be biologically non-relevant. (RIFM, 2016b). Under the conditions of the study, diethyl malonate was not mutagenic in the Ames test.

The clastogenic activity of diethyl malonate 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 malonate in DMSO at concentrations up to 1602 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Diethyl malonate did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2016c). Under the conditions of the study, diethyl malonate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/15/17.

10.1.2. Repeated dose toxicity

The margin of exposure for diethyl malonate 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 malonate. Read-across material dimethyl malonate (CAS # 108-59-8; see section V) has sufficient repeated dose toxicity data. The repeated dose toxicity of dimethyl malonate (DMM) was evaluated in a GLP-compliant OECD 422 combined repeated dose with reproduction/developmental screening test in Wistar rats. In this study, groups of 10 rats/sex/dose were administered daily via oral gavage with test material DMM at doses of 0, 100, 300, or 1000 mg/kg/day, 7 days per week. Five additional control and high-dose animals of each sex were included as recovery groups. Males received a total of 39 days of treatment, which included 2 weeks prior to mating, during mating, and approximately 2 weeks post-mating. Females were treated an average of 51 days (± 7 days), which included 2 weeks prior to mating, during mating, throughout pregnancy, and up to lactation day 4. Recovery animals were treated for 39 days, followed by a post-exposure observation period of 14 days. There were no effects of treatment on the liver weights or clinical chemistry parameters among treated animals. However, there was an increase in histopathological hepatocellular hypertrophy among treated animals. There were no treatment-related alterations reported among treated animals, except for a statistically significantly increased incidence of hepatocellular hypertrophy among high-dose animals. Since there were no reported increases in liver weights, and due to the lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage or clinical chemistry alterations, the incidences of hepatocellular hypertrophy were considered to be adaptive in nature and not adverse (Hall et al., 2012). Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: Dimethyl malonate).

A default safety factor of 3 is used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the diethyl malonate MOE for the repeated dose toxicity endpoint can be calculated by dividing the dimethyl malonate NOAEL in mg/kg/day by the total systemic exposure to diethyl malonate, 333/0.0099 or 33636.

In addition, the total systemic exposure to diethyl malonate (9.9 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 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.

Additional References: Posternak et al., 1969; OECD, SIDS Initial Assessment Report For SIAM 20 (Malonic Acid Diesters: Dimethylmalonate).

Literature Search and Risk Assessment Completed On: 09/08/17.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on diethyl malonate. Read-across material dimethyl malonate (CAS # 108-59-8; see section V) has sufficient reproductive toxicity data. The reproductive toxicity of DMM was evaluated in a GLP-compliant OECD 422 combined repeated dose with reproduction/developmental screening test in Wistar rats. In this study, groups of 10 rats/sex/dose were administered daily via oral gavage with test material dimethyl malonate at doses of 0, 100, 300, or 1000 mg/kg/day, 7 days per week. Five additional control and high-dose animals of each sex were included as recovery groups. Males received a total of 39 days of treatment, which included 2 weeks prior to mating, during mating, and approximately 2 weeks post mating. Females were treated an average of 51 days (± 7 days), which included 2 weeks prior to mating, during mating, throughout pregnancy, and up to lactation day 4. Recovery animals were treated for 39 days followed by a post-exposure observation period of 14 days. There were no treatment-related alterations observed for any of the fertility or developmental toxicity parameters assessed. Thus, the NOAEL for fertility and developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: dimethyl malonate).

Therefore, the diethyl malonate MOE for the reproductive toxicity endpoint can be calculated by dividing the dimethyl malonate NOAEL in mg/kg/day by the total systemic exposure to diethyl malonate, 1000/0.0099 or 101010.

In addition, the total systemic exposure to diethyl malonate (9.9 μg/kg/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: OECD, SIDS Initial Assessment Report For SIAM 20 (Malonic Acid Diesters: Dimethylmalonate, 108-59-8; Diethylmalonate, 105-53-3).

Literature Search and Risk Assessment Completed On: 09/08/17.

10.1.4. Skin sensitization

Based on the existing data and read-across material pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0), diethyl malonate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited studies are available on diethyl malonate. Based on the existing data and read-across material pentanedioic acid, 1,5-dimethyl ester, diethyl malonate does not present a safety concern for skin sensitization under the current

declared levels of use. The chemical structures of these materials indicate that they 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, read-across material pentanedioic acid, 1,5-dimethyl ester was found to be non-sensitizing up to 100% (ECHA Dossier: pentanedioic acid, 1,5-dimethyl ester). In a guinea pig maximization test, read-across material pentanedioic acid, 1,5-dimethyl ester did not present reactions indicative of sensitization (ECHA Dossier: pentanedioic acid, 1,5-dimethyl ester). In a human repeat insult patch test (HRIPT) conducted with 41 subjects, diethyl malonate did not induce sensitization reactions at 20% (20000μg/cm^2) (RIFM, 1978). In a human maximization test, diethyl malonate did not induce sensitization reactions at 4% (2760μg/cm^2) in 23 subjects (RIFM, 1975).

Based on the weight of evidence from structural analysis, human studies, and read-across material pentanedioic acid, 1,5-dimethyl ester, diethyl malonate does not present a safety concern for skin sensitization under the current declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, diethyl malonate 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 malonate 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 malonate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/17.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There is insufficient inhalation data available on diethyl malonate. Based on the Creme RIFM Model, the inhalation exposure is 0.17 mg/day. This exposure is 8.2 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: Smyth et al., 1969.

Literature Search and Risk Assessment Completed On: 08/03/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of diethyl malonate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA 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 malonate 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 (EPI Suite, 2012) did not identify diethyl malonate as possibly being either 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 BIOWIN 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), diethyl malonate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2011**:** The ready biodegradability of the test material was evaluated using a Manometric Respirometry Test according to the OECD 301F method. Under the conditions of this study, biodegradation of 109% was observed after 28 days.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Diethyl malonate has been registered under REACH, and the following additional data is reported:

Daphnia magna acute toxicity study was conducted according to the EU Method C.2 under static conditions, and the 48-h EC50 was reported to be 179 mg/L.

A 72-h Algae growth inhibition study was conducted according to the 88/302/EEC method, and the EC50 was reported to be 508 mg/L and > 800 mg/L based on biomass and growth rate, respectively.

10.2.3. Risk assessment refinement

Since diethyl malonate has passed the screening criteria, measured data is included in the document 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**)	1956			1,000,000	1.956	

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

Exposure	Europe	North America
Log K_{OW} used	0.9	0.9
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 1.956 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at the screening-level and therefore the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 08/09/17.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- 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://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** 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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.059.

Appendix

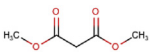
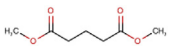
Read-across justification

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 structural similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (EPI Suite, 2012).
- 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	Read-across Material
Principal Name	Diethyl malonate	Dimethyl malonate	Pentanedioic acid, 1,5-dimethyl ester
CAS No.	105-53-3	108-59-8	1119-40-0
Structure			
Similarity (Tanimoto Score)		0.63	0.62
Read-across Endpoint		• Repeated dose • Reproductive	• Skin sensitization
Molecular Formula	$C_7H_{12}O_4$	$C_5H_8O_4$	$C_7H_{12}O_4$
Molecular Weight	160.17	132.12	160.17
Melting Point (°C, EPI Suite)	−83.29	−107.58	−83.29
Boiling Point (°C, EPI Suite)	166.02	121.41	166.02
Vapor Pressure (Pa @ 25 °C, EPI Suite)	48.1	120	23.7
Log_{KOW} (KOWWIN v1.68 in EPI Suite)	0.96	−0.05	0.62
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	23200	99510	59000
J_{max} (mg/cm^2/h, SAM)	69.462	150.459	98.151
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.36E-007	4.17E-007	7.36E-007
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Toxicant (low reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found		• No alert found
Protein Binding (OECD)	• No alert found		• No alert found
Protein Binding Potency	• Not possible to classify		• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on diethyl malonate (CAS # 105-53-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, dimethyl malonate (CAS # 108-59-8) and pentanedioic acid, 1,5-dimethyl ester (CAS # 1190-40-0) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Dimethyl malonate (CAS # 108-59-8) was used as a read-across analog for the target material diethyl malonate (CAS # 105-53-3) for the repeated dose and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of esters.
  - The target material and the read-across analog share a common carboxylic acid ester fragment.
  - The key difference between the target material and the read-across analog is that the target is a diethyl ester of malonic acid while the read-across is a dimethyl ester of malonic acid. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the carboxylic acid ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoints are consistent between the target material and the read-across analog.
  - The read-across analog is predicted to be a toxicant by CAESAR model for developmental toxicity. All the other alerts are negative. According to these predictions, the read-across analog is expected to be more reactive when compared to the target material. The data described in the developmental toxicity section above shows that the read-across analog has an adequate margin of exposure at the current level of use.

Therefore, the predictions are superseded by data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Pentanedioic acid, 1,5-dimethyl ester (CAS # 1190-40-0) was used as a read-across analog for the target material diethyl malonate (CAS # 105-53-3) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of esters.
  - The target material and the read-across analog share a common carboxylic acid ester fragment.
  - The key difference between the target material and the read-across analog is that the target is a diethyl ester of malonic acid while the read-across is a dimethyl ester of pentanedioic acid. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the carboxylic acid ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

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