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Short Review

RIFM fragrance ingredient safety assessment, ethyl 2,4-dimethyldioxolane-2-acetate, CAS Registry Number 6290-17-1

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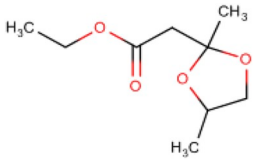


Abbreviation/Definition List:

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
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 as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Ethyl 2,4-dimethyldioxolane-2-acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that ethyl 2,4-dimethyldioxolane-2-acetate is not genotoxic. Data from read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1) show that ethyl 2,4-dimethyldioxolane-2-acetate has no safety concerns for skin sensitization under the current, declared levels of use. Data from read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1) provide a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to ethyl 2,4-dimethyldioxolane-2-acetate is below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; ethyl 2,4-dimethyldioxolane-2-acetate is not expected to be phototoxic/photoallergenic. For the environmental endpoints, ethyl 2,4-dimethyldioxolane-2-acetate is not PBT as per the IFRA Environmental Standards, and its risk quotients (i.e., PEC/PNEC) for the aquatic environment based on its current volume of use in Europe and North America are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2002b; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methyl-1,3-dioxolane-2-acetate; ECHA, 2013)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methyl-1,3-dioxolane-2-acetate; ECHA, 2013)
Skin Sensitization: No safety concerns at current, declared use levels.	RIFM, (2013b)
Phototoxicity/Photoallergenicity: Not expected to be 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: 10% (OECD 301D)	RIFM, (2002c)
Bioaccumulation: Screening-level: 6.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 462.5 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: 462.5 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.4625 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Ethyl 2,4-dimethyldioxolane-2-acetate
2. **CAS Registry Number:** 6290-17-1
3. **Synonyms:** 1,3-Dioxolane-2-acetic acid, 2,4-dimethyl-, ethyl ester; Ethyl 2,4-dimethyl-1,3-dioxolane-2-acetate; ｴﾁﾙ-2,4-ｼﾞﾒﾁﾙ-1,3-ｼﾞｵｷｿﾗﾝ-2-ｱｾﾃｰﾄ; cis- and trans-Ethyl 2,4-dimethyl-1,3-dioxolane-2-acetate; Z- and E-Ethyl 2,4-dimethyl-1,3-dioxolane-2-acetate; Dimethyldioxolan; Ethyl (2,4-dimethyl-1,3-dioxolan-2-yl)acetate; Fraistone; Ethyl 2,4-dimethyldioxolane-2-acetate
4. **Molecular Formula:** $C_9H_{16}O_4$
5. **Molecular Weight:** 188.22
6. **RIFM Number:** 5117
7. **Stereochemistry: Stereochemistry:** Isomer not specified. Two stereocenters and 4 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 231.07 °C (US EPA, 2012a)
2. **Flash Point:** 75 °C (GHS)
3. **Log K_{OW}:** 1.72 (US EPA, 2012a)
4. **Melting Point**: 32.66 °C (US EPA, 2012a)
5. **Water Solubility:** 1712 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 1.04800 to 1.05400 @ 25.00 °C*; 1.03900 to 1.04700 @ 20.00 °C*
7. **Vapor Pressure:** 0.0351 mm Hg @ 20 °C (US EPA, 2012a), 0.0596 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a fruity odor*

*http://www.thegoodscentscompany.com/data/rw1005422.html, 12/06/17.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.04% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00051 mg/kg/day or 0.037 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0027 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; 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 III, High

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1)
   c. **Reproductive Toxicity:** Ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1)
   d. **Skin Sensitization:** Ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1)
   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)

Ethyl 2,4-dimethyldioxolane-2-acetate is not reported to occur in foods by the VCF.*

*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

Available; accessed 08/06/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, ethyl 2,4-dimethyldioxolane-2-acetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Ethyl 2,4-dimethyldioxolane-2-acetate was

assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

The mutagenic activity of ethyl 2,4-dimethyldioxolane-2-acetate 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, TA1535, and TA102 were treated with ethyl 2,4-dimethyldioxolane-2-acetate 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 concentration in the presence or absence of S9 (RIFM, 2002b). Under the conditions of the study, ethyl 2,4-dimethyldioxolane-2-acetate was not mutagenic in the Ames test.

The clastogenic activity of ethyl 2,4-dimethyldioxolane-2-acetate 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 ethyl 2,4-dimethyldioxolane-2-acetate in DMSO at concentrations up to 1882 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Ethyl 2,4-dimethyldioxolane-2-acetate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, ethyl 2,4-dimethyldioxolane-2-acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl 2,4-dimethyldioxolane-2-acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/21/17.

10.1.2. Repeated Dose Toxicity

The margin of exposure for ethyl 2,4-dimethyldioxolane-2-acetate is adequate repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on ethyl 2,4-dimethyldioxolane-2-acetate. Read-across material, ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1; see section V) has sufficient repeated dose toxicity data. An OECD 422 oral gavage study was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose were administered read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate at doses of 0 (water), 100, 300, or 1000 mg/kg/day. The males received the test material for 2 weeks before pairing, during the 2-week pairing period, and until euthanasia (at least 5 weeks in total). Females received the test material for 2 weeks before mating, during the 2-week pairing period, during gestation, and during lactation until day 5 postpartum inclusive (or until euthanasia). There were no test material–related mortalities among treated animals. One death was reported among low-dose females, which was attributed to gavage error. There were no other treatment-related alterations reported among treated animals up to the highest dose tested. Thus, the NOAEL for the repeated dose toxicity endpoint was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the ethyl 2,4-dimethyldioxolane-2-acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl 2-methyl-1,3-dioxolane-2-acetate NOAEL in mg/kg/day by the total systemic exposure to ethyl 2,4-dimethyldioxolane-2-acetate, 333/0.0027 or 123333.

*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: 11/30/17.

10.1.3Reproductive Toxicity

The margin of exposure for ethyl 2,4-dimethyldioxolane-2-acetate 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 ethyl 2,4-dimethyldioxolane-2-acetate. Read-across material, ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1; see section V), has sufficient reproductive toxicity data. An OECD 422 oral gavage study was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose were administered ethyl 2-methyl-1,3-dioxolane-2-acetate at doses of 0 (water), 100, 300, or 1000 mg/kg/day. The males received the test material for 2 weeks before pairing, during the 2-week pairing period, and until euthanasia (at least 5 weeks in total). Females received the test material for 2 weeks before mating, during the 2-week pairing period, during gestation, and during lactation until day 5 postpartum inclusive (or until euthanasia). There was no test material–related mortality among treated animals. One death was reported among low-dose females, which was attributed to gavage error. There were no treatment-related effects on mating and fertility parameters among treated animals. There were no treatment-related effects on the distribution of pups found dead and/or cannibalized, and there were no treatment-related findings at pup examinations. Furthermore, there were no toxicologically significant effects on live birth, viability, and lactation indices. There was a tendency towards a decrease in the mean body weight and mean bodyweight changes in pups at 1000 mg/kg/day; this finding was considered to be test material–related but of minor toxicological significance since the differences were low and remained within the historical control ranges. The NOAEL for the reproductive toxicity endpoint was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

Therefore, the ethyl 2,4-dimethyldioxolane-2-acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the ethyl 2-methyl-1,3-dioxolane-2-acetate NOAEL in mg/kg/day by the total systemic exposure to ethyl 2,4-dimethyldioxolane-2-acetate, 1000/0.0027 or 370370.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/17.

10.1.4. Skin sensitization

Based on the existing data and read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1), ethyl 2,4-dimethyldioxolane-2-acetate 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 for ethyl 2,4-dimethyldioxolane-2-acetate. Based on the read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1), ethyl 2,4-dimethyldioxolane-2-acetate 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 (Toxtree 2.6.13; OECD toolbox v3.4). In guinea pigs, a maximization test did not present reactions indicative of sensitization with ethyl 2,4-dimethyldioxolane-2-acetate (RIFM, 2002a). In a murine local lymph node assay, read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate was found to be negative up to a maximum tested concentration of 100%, which resulted in Stimulation

Index (SI) of 0.85 (RIFM, 2013b). In 2 human maximization tests, no skin sensitization reactions were observed with read-across analog ethyl 2-methyl-1,3-dioxolane-2-acetate (RIFM, 1978; RIFM, 1979). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 581 and 11628 μg/cm^2 of read-across material ethyl 2-methyl-1,3-dioxolane-2-acetate in ethanol, no reactions indicative of sensitization were observed in any of the 42 and 45 volunteers, respectively (RIFM, 1971; RIFM, 1964).

Based on the weight of evidence from structural analysis, animal studies, and read-across material ethyl 2-methyl-1,3-dioxolane-2-acetate, ethyl 2,4-dimethyldioxolane-2-acetate 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: 10/25/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl 2,4-dimethyldioxolane-2-acetate 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 ethyl 2,4-dimethyldioxolane-2-acetate 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 lack of absorbance, ethyl 2,4-dimethyldioxolane-2-acetate 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: 10/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for ethyl 2,4-dimethyldioxolane-2-acetate is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on ethyl 2,4-dimethyldioxolane-2-acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.037 mg/day. This exposure is 12.7 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl 2,4-dimethyldioxolane-2-acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{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, ethyl 2,4-dimethyldioxolane-2-acetate 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 ethyl 2,4-dimethyldioxolane-2-acetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's 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), ethyl 2,4-dimethyldioxolane-2-acetate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2002c: The ready biodegradability of the test material was evaluated in a Closed Bottle Test according to the OECD 301D guidelines. Biological Oxygen Demand (BOD) bottles containing 4 mg/L of ethyl 2,4-dimethyldioxolane-2-acetate and mineral nutrient solution inoculated with activated sludge were incubated for 28 days. Under the conditions of this study, biodegradation of 10% was observed after 28 days.

10.2.2.2. Ecotoxicity. RIFM, 2002d: A *Daphnia magna* acute immobilization study (limit test) was conducted according to the OECD 202I method under static conditions. The percentage immobility was determined in the tested limit concentration and the control after 24 and 48 h. There was no biologically significant effect determined in the saturated solution at 24 or 48 h.

10.2.3. Other available data

Ethyl 2,4-dimethyldioxolane-2-acetate has been registered under REACH with no additional data at this time.

10.2.4. Risk assessment refinement

Since Ethyl 2,4-dimethyldioxolane-2-acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	462.5			1000000	0.4625	

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

Exposure	Europe	North America
Log K_{ow} used	1.1	1.1
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 the available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.4625 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/28/17.

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. The links listed above were active as of 06/12/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110590.

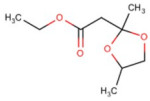
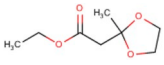
Appendix

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 were 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	Ethyl 2,4-dimethyldioxolane-2-acetate	Ethyl 2-methyl-1,3-dioxolane-2-acetate
CAS No.	6290-17-1	6413-10-1
Structure		
Similarity (Tanimoto Score)		0.85
Read-across Endpoint		• Repeated dose • Reproductive • Skin sensitization
Molecular Formula	$C_9H_{16}O_4$	$C_8H_{14}O_4$
Molecular Weight	188.23	174.2
Melting Point (°C, EPI Suite)	32.66	25.25
Boiling Point (°C, EPI Suite)	231.07	217.4
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.95	18.1
Log Kow (KOWWIN v1.68 in EPI Suite)	1.72	0.8[1]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1712	124800[2]
J_{max} (μg/cm^2/h, SAM)	60.04	194.272
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.67E-002	1.26E-002
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-Toxicant (low reliability)	• Non-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

1. RIFM, 1997.
2. RIFM, 2012.

Summary

There are insufficient toxicity data on ethyl 2,4-dimethyldioxolane-2-acetate (CAS # 6290-17-1). 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, ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 2-methyl-1,3-dioxolane-2-acetate (CAS # 6413-10-1) was used as a read-across analog for the target material ethyl 2,4-dimethyldioxolane-2-acetate (CAS # 6290-17-1) for the repeated dose, reproductive toxicity, and skin sensitization endpoints.
  - The target substance and the read-across analog are structurally similar and belong to the class of ketals.
  - The target substance and the read-across analog share a common heterocyclic acetal fragment and an additional ester functional group.
  - The key structural difference between the target substance and the read-across analog is that the target substance has 2 methyl substituents on the heterocyclic acetal fragment, whereas the read-across analog only has one methyl substituent. This structural difference is toxicologically insignificant.
  - Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - 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 OECD QSAR 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.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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