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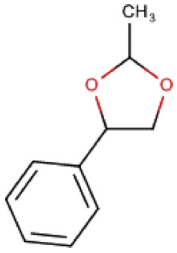
Short Review

RIFM fragrance ingredient safety assessment, 2-methyl-4-phenyl-1,3-dioxolane, CAS Registry Number 33941-99-0

A.M. Api[a], F. Belmonte[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

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

Version: 121818. This version replaces any previous versions.
Name: 2-Methyl-4-phenyl-1,3-dioxolane
CAS Registry Number: 33941-99-0



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, 2017; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
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

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

2-Methyl-4-phenyl-1,3-dioxolane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-methyl-4-phenyl-1,3-dioxolane is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to 2-methyl-4-phenyl-1,3-dioxolane is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). Data from the target material and the read-across analog phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal (CAS # 67633-94-7) show that there are no safety concerns for 2-methyl-4-phenyl-1,3-dioxolane for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-methyl-4-phenyl-1,3-dioxolane is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-methyl-4-phenyl-1,3-dioxolane was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2015b; RIFM, 2013)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	(RIFM, 2006)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	ECHA REACH Dossier: 2-Benzyl-4,4,6-trimethyl-1,3-dioxane
Skin Sensitization: Does not present a concern for skin sensitization under the current, declared levels of use.	ECHA, 2017
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 0% (301 C)	RIFM, (2000b)
Bioaccumulation: Screening-level: 6.578 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 151.-3 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: 151-.3 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.1513 μg/L

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

1. Identification

1. **Chemical Name:** 2-Methyl-4-phenyl-1,3-dioxolane
2. **CAS Registry Number:** 33941-99-0
3. **Synonyms:** 1,3-dioxolane, 2-**methyl**-4-phenyl; Jacinthaflor; 2-Methyl-4-phenyl-1,3-dioxolane
4. **Molecular Formula:** $C_{10}H_{12}O_2$
5. **Molecular Weight:** 164.2
6. **RIFM Number:** 6413
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 240.62 °C (EPI Suite), no boiling point up to the decomposition temperature of 110 °C at 993 hPa (RIFM, 2015d)
2. **Flash Point:** 102 °C (GHS), 97.5 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015e)
3. **Log K_{OW}**: 1.74 (EPI Suite), 2.**19** at 24.7 °C (RIFM, 2016a)
4. **Melting Point**: 21.18 °C (EPI Suite), **no** melting point at 993 hPa (RIFM, 2015d)
5. **Water Solubility:** 2119 mg/L (EPI **Suite**)
6. **Specific Gravity:** Not **Available**
7. **Vapor Pressure:** 0.0287 mm Hg @ 20 °C (EPI Suite v4.0), 0.0448 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant **absorbance** between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000\ L\ mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 **metric** ton per year (IFRA (International Fragrance Association), 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.04% (RIFM, 2015a)
3. **Inhalation Exposure*:** 0.00012 mg/kg/day or 0.0087 mg/day (RIFM, 2015a)
4. **Total Systemic Exposure**:** 0.00069 mg/kg/**day** (RIFM, 2015a)

*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: None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Phenylacetaldehyde 2,4-**dihydroxy**-2-methylpentane acetal (CAS # 67633-94-7)
   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 are available for inclusion in this safety assessment.

6.1. Additional References

None.

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

2-Methyl-4-phenyl-1,3-dioxolane 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 on 12/18/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-methyl-4-phenyl-1,3-dioxolane does not present a concern for genotoxicity.

10.1.2. Risk assessment

2-Methyl-4-phenyl-1,3-dioxolane was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2-methyl-4-phenyl-1,3-dioxolane has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA were treated with 2-methyl-4-phenyl-1,3-dioxolane 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, 2015b). Under the conditions of the study, 2-methyl-4-phenyl-1,3-dioxolane was not mutagenic in the Ames test.

The clastogenic activity of 2-methyl-4-phenyl-1,3-dioxolane 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 2-methyl-4-phenyl-1,3-dioxolane in DMSO at concentrations up to 1642 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up tp 785 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h 2-methyl-4-phenyl-1,3-dioxolane 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, 2013). Under the conditions of the study, 2-methyl-4-phenyl-1,3-dioxolane was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 2-methyl-4-phenyl-1,3-dioxolane does not present a concern for genotoxic potential.

Additional References: RIFM, 2015c.

Literature Search and Risk Assessment Completed On: 01/27/19.

10.1.3. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-methyl-4-phenyl-1,3-dioxolane or any read-across materials. The total systemic exposure to 2-methyl-4-phenyl-1,3-dioxolane is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on 2-methyl-4-phenyl-1,3-dioxolane or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-methyl-4-phenyl-1,3-dioxolane (0.69 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/31/19.

10.1.5. Reproductive toxicity

There are no reproductive toxicity data on 2-methyl-4-phenyl-1,3-dioxolane or on any read-across materials. The total systemic exposure to 2-methyl-4-phenyl-1,3-dioxolane is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.6. Risk assessment

There are no reproductive toxicity data on 2-methyl-4-phenyl-1,3-dioxolane or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-methyl-4-phenyl-1,3-dioxolane (0.69 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/07/19.

10.1.7. Skin sensitization

Based on the existing data and read-across material phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal (CAS # 67633-94-7), 2-methyl-4-phenyl-1,3-dioxolane does not present a concern for skin sensitization under the current, declared levels of use.

10.1.8. Risk assessment

Insufficient skin sensitization studies are available for 2-methyl-4-phenyl-1,3-dioxolane. Based on the existing data and read-across material phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal (CAS # 67633-94-7; see Section V), 2-methyl-4-phenyl-1,3-dioxolane is not considered a skin sensitizer. The chemical structures of these materials indicate that these materials would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), the read-across material, phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal, was found to be non-sensitizing when tested up to 100% (https://echa.europa.eu/en/registration-dossier/-/registered-dossier/19416/1, ECHA, 2017). In a guinea pig maximization test using the target material did not present reactions indicative of sensitization (https://echa.europa.eu/registration-dossier/-/registered-dossier/18277/7/5/2, ECHA, 2016a; RIFM, 2000a). In a human maximization test, no skin sensitization reactions were observed with the read-across material. (RIFM, 1979). In a confirmatory human repeat insult patch test (HRIPT) with 5% (3875.97 μg/cm^2) with 38 male and female volunteer subjects, the read-across material did not elicit any reactions indicative of skin sensitization (RIFM, 1965). Additionally, in another HRIPT using 5555.6 μg/cm^2 of the target material, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2006). Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal, 2-methyl-4-phenyl-1,3-dioxolane does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1967.

Literature Search and Risk Assessment Completed On: 02/03/19.

10.1.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-methyl-4-phenyl-1,3-dioxolane would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for 2-methyl-4-phenyl-1,3-dioxolane in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, 2-methyl-4-phenyl-1,3-dioxolane does not present a concern for phototoxicity or photoallergenicity.

10.1.11. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) for 2-methyl-4-phenyl-1,3-dioxolane were obtained. The spectra indicate minor 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: 01/15/19.

10.1.12. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-methyl-4-phenyl-1,3-dioxolane is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.13. Risk assessment

There are no inhalation data available on 2-methyl-4-phenyl-1,3-dioxolane. Based on the Creme RIFM Model, the inhalation exposure is 0.0087 mg/day. This exposure is 54 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: 01/28/19.

11. Environmental endpoint summary

11.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-4-phenyl-1,3-dioxolane 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, 2-methyl-4-phenyl-1,3-dioxolane 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 2-methyl-4-phenyl-1,3-dioxolane as possibly being 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.

11.1.1. Risk assessment

Based on the current Volume of Use (2015), 2-methyl-4-phenyl-1,3-dioxolane presents no risk to the aquatic compartment in the screening-level assessment.

11.1.2. Biodegradation

RIFM, 2000b: The biodegradability of the test material was determined with the BOD test for insoluble substances (BODIS). The degradation process was followed by measuring the oxygen consumption in closed vessel for 28 days. Degradation of 67.4% was observed after 28 days.

RIFM, 2000c: The ready biodegradability of the test material was determined according to the OECD 301 C method. No degradation was observed after 28 days.

11.1.3. Ecotoxicity

RIFM, 2016b: The *Daphnia* acute immobilization test was conducted on the test material according to the OECD 202 method. The 48-h EC50 was determined to be greater than 100 mg/L.

RIFM, 2016c: The algae growth inhibition test was conducted on the test material according to the OECD 201 method. The 72-h EC50 was determined to be greater than 69.2 mg/L.

11.1.4. Other available data

2-Methyl-4-phenyl-1,3-dioxolane has been registered for REACH with no additional data available at this time.

11.1.5. Risk assessment refinement

Since 2-methyl-4-phenyl-1,3-dioxolane 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*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	151.3	X	X	1,000,000	0.1513	X

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.19	2.19
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 material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.1513 μg/L. The revised PEC/PNECs for EU and North America 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: 01/23/19.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110843.

Appendix

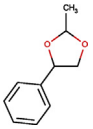
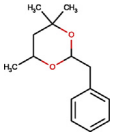
Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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, 2016b).

- 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US ECHA, 2012a).
  - Jmax values were calculated using RIFM's Skin Absorption Model (SAM).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	2-Methyl-4-phenyl-1,3-dioxolane	Phenylacetaldehyde 2,4-dihydroxy-2-methyl-pentane acetal
CAS No.	33941-99-0	67633-94-7
Structure		
Similarity (Tanimoto Score)		0.49
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{10}H_{12}O_2$	$C_{14}H_{20}O_2$
Molecular Weight	164.20	220.31
Melting Point (°C, EPI Suite)	21.18	67.55
Boiling Point (°C, EPI Suite)	240.62	294.62
Vapor Pressure (Pa @ 25 °C, EPI Suite)	5.97	0.138
Log K_{OW}(KOWWIN v1.68 in EPI Suite)	1.74	3.60
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2119	29.01
J_{max} (μg/cm^2/h, SAM)	37.764	11.663
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.629E-001	7.52E-001
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 according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
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 v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-methyl-4-phenyl-1,3-dioxolane (CAS # 33941-99-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal (CAS # 67633-94-7) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal (CAS # 67633-94-7) was used as a read-across analog for the target material 2-methyl-4-phenyl-1,3-dioxolane (CAS # 33941-99-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic cyclic acetal.
  - o The target material and the read-across analog share a cyclic acetal group connected to a phenyl ring.
  - o The key difference between the target material and the read-across analog is that the target material consists of a 2-methyldioxolane ring connected to a phenyl ring in position 4, while the read-across analog consists of an 4,4,6-trimethyl-*m*-dioxane ring connected to a benzyl group in position 2. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o 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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