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RIFM fragrance ingredient safety assessment, phenylacetaldehyde dimethyl acetal, CAS Registry Number 101-48-4

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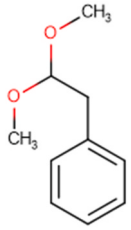
Name: Phenylacetaldehyde dimethyl acetal



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CAS Registry Number: 101-48-4

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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(*continued*)

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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
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 Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
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.

Phenylacetaldehyde dimethyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that phenylacetaldehyde dimethyl acetal is not genotoxic. Data on phenylacetaldehyde dimethyl acetal provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for phenylacetaldehyde dimethyl acetal for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; phenylacetaldehyde dimethyl acetal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to phenylacetaldehyde dimethyl acetal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; phenylacetaldehyde dimethyl acetal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1999d; RIFM, 2001; RIFM, 2002; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM, (2017)
Reproductive Toxicity: Developmental toxicity NOAEL = 600 mg/kg/day. Fertility NOAEL = 600 mg/kg/day.	RIFM, (2017)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 2016d; RIFM, 1982b; RIFM, 1982a; RIFM, 1965; RIFM, 1971)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 57% (OECD 302C)	RIFM, (1999a)
Bioaccumulation: Screening-level: 8.72 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 64.52 mg/L	(ECOSAR; US EPA, 2012b)

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: 96-h Algae EC50: 64.52 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 6.452 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** Phenylacetaldehyde dimethyl acetal
2. **CAS Registry Number:** 101-48-4
3. **Synonyms:** Benzene, (2,2-dimethoxyethyl)-; 1,1-Dimethoxy-2-phenylethane; Lilas Vert; PADIMA; P.A.D.M.A.; Rosal; α-Tolyl aldehyde dimethyl acetal; Vertodor; Viridine; Phenyl Acetic Aldehyde Dimethyl Acetal; ﾌｪﾆﾙｱｾﾄｱﾙﾃﾞﾋﾄﾞｱﾙｷﾙ(C = 1～2)ｱｾﾀｰﾙ; (2,2-Dimethoxyethyl)benzene; Phenylacetaldehyddimethylacetat; Phenylacetaldehyde dimethyl acetal
4. **Molecular Formula:** $C_{10}H_{14}O_2$
5. **Molecular Weight:** 166.22 g/mol
6. **RIFM Number:** 198
7. **Stereochemistry:** Isomer not specified. One chiral center is present, and a total of 2 enantiomers are possible.

2. Physical data

1. **Boiling Point:** 220 °C (Fragrance Materials Association [FMA]), 219.76 °C (EPI Suite), 218 °C at 1013 hPa (RIFM, 2016a)
2. **Flash Point:** 82 °C (Globally Harmonized System), 180 °F (FMA), 91.0 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2016b)
3. **Log K_{OW}:** 2.3 at 35 °C (RIFM, 1999b), 1.93 (EPI Suite), 2.23 at 24.7 °C (RIFM, 2016c)

4. **Melting Point**: −0.08 °C (EPI Suite), no melting point down to −100 °C at 993 hPa (RIFM, 2016a)
5. **Water Solubility:** 1439 mg/L (EPI Suite)
6. **Specific Gravity:** 1.002–1.008 (FMA), 1.000–1.006 (FMA)
7. **Vapor Pressure:** 0.0875 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.133 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless to pale yellow liquid having a strong "green" odor

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.045% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00035 mg/kg/day or 0.025 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2019)

*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; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

6.1. Cramer classification

Class I, Low.

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. Analogs selected

a. **Genotoxicity:** Weight of evidence (WoE): *p*-(2,2-Dimethoxyethyl) toluene (CAS # 42866-91-1)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix.

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurence

Phenylacetaldehyde dimethyl acetal is reported to occur in the following foods by the VCF*:

Cocoa category.

*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.

9. REACH Dossier

Available; accessed on 10/26/21 (ECHA, 2017).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Phenylacetaldehyde dimethyl acetal 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, 2010). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of phenylacetaldehyde dimethyl acetal has been evaluated in 2 bacterial reverse mutation assays 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, TA1537, and TA102 were treated with phenylacetaldehyde dimethyl acetal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Statistically significant and dose-dependent increases were observed in TA1535 in the absence of S9 (RIFM, 1999d). A second GLP/OECD guideline study was conducted in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 at doses up to 5000 μg/plate. Statistically significant and dose-dependent increases were observed in TA1535 in the absence of S9 (RIFM, 2001). Based on this information, phenylacetaldehyde dimethyl acetal was considered mutagenic in the Ames test. To further investigate the adverse findings, a mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells (V79) were treated with phenylacetaldehyde dimethyl acetal in DMSO at concentrations up to 10 nM for 3.5 and 24 h. Effects were evaluated both with and without metabolic activation. No

significant increases in the frequency of mutant colonies were observed with any dose of the test material, either with or without metabolic activation (RIFM, 2002). The cell line used (eukaryotic) in this assay closely recapitulates DNA repair mechanisms found in humans and makes these study results more biologically relevant in the assessment of phenylacetaldehyde dimethyl acetal compared to strain-specific increases in a bacterial assay. Additionally, OASIS TIMES predicted phenylacetaldehyde dimethyl acetal to be negative in the *in vitro* Ames simulator and the *in vivo* Comet simulator (OASIS TIMES v2.27.19.3). Additional weight of evidence (WoE) can be made by read-across to *p*-(2,2-dimethoxyethyl)toluene (CAS # 42866-91-1). This material 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 *p*-(2,2-dimethoxyethyl)toluene in DMSO at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increases in the mean number of revertant colonies were observed at any dose tested in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, *p*-(2,2-dimethoxyethyl) toluene was not mutagenic in the Ames test.

The clastogenic activity of phenylacetaldehyde dimethyl acetal 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 phenylacetaldehyde dimethyl acetal in solvent DMSO at concentrations up to 1662 μg/mL in the presence and absence of metabolic activation (S9) at the 4-h and 20-h timepoints. Phenylacetaldehyde dimethyl acetal did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2015b). Under the conditions of the study, phenylacetaldehyde dimethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test.

The adverse test results obtained in the Ames test were considered to be not biologically relevant since 2 *in vitro* mammalian cell assays, a mammalian cell gene mutation assay (HPRT) and an *in vitro* micronucleus test were negative. Negative results in mammalian cell tests covering clastogenic, aneugenic, and gene mutation endpoints could indicate that a material producing adverse Ames data is not likely to be carcinogenic or genotoxic *in vivo* (Kirkland et al., 2014). Additionally, read-across material *p*-(2,2-dimethoxyethyl)toluene (CAS # 42866-91-1) also gave negative results in an Ames assay. Therefore, phenylacetaldehyde dimethyl acetal was not expected to be mutagenic to mammalian cells.

Based on the current existing data, phenylacetaldehyde dimethyl acetal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

The MOE for phenylacetaldehyde dimethyl acetal is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on phenylacetaldehyde dimethyl acetal. An OECD 422/GLP combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were exposed to the test material phenylacetaldehyde dimethyl acetal at doses of 60, 200, or 600 mg/kg/day via oral gavage in corn oil once daily and 7 days per week. Males were treated for 50 days (prior to mating for 2 weeks, during 2 weeks of mating, and 22 days of post-mating), and females were treated for 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. In addition, males and females of the recovery groups were dosed for 50 days.

No treatment related mortality was observed in any dose group. Two females (dams) were found in a moribund state dosed with 60 mg/kg/day. However, this state was considered to be incidental because there was no dose-dependency, and it was observed in the low-dose group only. In general, systemic observations, treatment-related salivation was observed in both sexes (3 males and 2 females) of the high-dose group, but the effect was not considered toxicologically significant. No treatment-related adverse effects were observed for body weights, food consumption, estrous cycle, sensory function, motor activity, urinalysis, hematology, clinical chemistry, and thyroid hormone analysis in animals of both sexes. In the moribund dams, tubular degeneration and orange-colored casts in renal tubules were observed. However, these were not considered to be test material-related effects since the lesions were observed only at 60 mg/kg/day. The absolute and/or relative organ weights of the liver were significantly increased in males in the high-dose group and females in the mid- and high-dose groups. Hepatocellular hypertrophy was observed in both sexes in the mid- and high-dose groups. Centrilobular hepatocellular hypertrophy was regarded as an adaptive response to the test material. Thus, the NOAEL for repeated dose toxicity was considered to be 600 mg/kg/day, the highest dose tested (RIFM, 2017).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for repeated dose toxicity is 600/3 or 200 mg/kg/day.

Therefore, the phenylacetaldehyde dimethyl acetal MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenylacetaldehyde dimethyl acetal NOAEL in mg/kg/day by the total systemic exposure to phenylacetaldehyde dimethyl acetal, 200/0.0016, or 125000.

In addition, the total systemic exposure to phenylacetaldehyde dimethyl acetal (1.6 μg/kg/day) is below the TTC (30 μg/kg/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: None.

Literature Search and Risk Assessment Completed On: 10/12/21.

11.1.3. Reproductive toxicity

The MOE for phenylacetaldehyde dimethyl acetal is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on phenylacetaldehyde dimethyl acetal. An OECD 422/GLP combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were exposed to the test material, phenylacetaldehyde dimethyl acetal, at doses of 60, 200, or 600 mg/kg/day via oral gavage in corn oil once daily and 7 days per week. Males were treated for 50 days (prior to mating for 2 weeks, during 2 weeks of mating, and during 22 days of post-mating), and females were treated for 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. In addition, males and females of the recovery groups were dosed for 50 days.

No mortality was observed in any dose group. Two females (dams) of the main group were found in a moribund state at 60 mg/kg/day. However, these moribund animals were considered to be incidental because there was no dose-dependency, and these were observed in the low-dose group only. No treatment-related adverse effects were

observed in the estrous cycle, mating period, mating index, gestation period, male and female fertility indexes, gestation index, post-implantation loss rate, live birth index, mean litter size, external examination of pups, body weights of pups, the sex ratio of pups, and viability index of postnatal days 0 and 4. In the main group, the absolute organ weight of the testis was significantly decreased in males at 600 mg/kg/day. However, it was considered to have little toxicological significance since there were no treatment-related histopathological changes in the testis and epididymis. No treatment-related effects were noted in the results of the anogenital distance (AGD) index of pups, nipple retention of male pups, and T4 of pups. Thus, the NOAEL for developmental toxicity and fertility was considered to be 600 mg/kg/day, the highest dose tested (RIFM, 2017).

Therefore, the phenylacetaldehyde dimethyl acetal MOE for the reproductive toxicity endpoint can be calculated by dividing the phenylacetaldehyde dimethyl acetal NOAEL in mg/kg/day by the total systemic exposure to phenylacetaldehyde dimethyl acetal, 600/0.0016, or 127605.

In addition, the total systemic exposure to phenylacetaldehyde dimethyl acetal (1.6 μg/kg/day) is below the TTC (30 μg/kg/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: None.

Literature Search and Risk Assessment Completed On: 10/12/21.

11.1.4. Skin sensitization

Based on the existing data, phenylacetaldehyde dimethyl acetal does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on existing data, phenylacetaldehyde dimethyl acetal does not present a concern for skin sensitization. The chemical structure of phenylacetaldehyde dimethyl acetal indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), phenylacetaldehyde dimethyl acetal was found to be non-sensitizing up to 100% (ECHA, 2017; RIFM, 2016d). In 2 separate guinea pig maximization tests, phenylacetaldehyde dimethyl acetal did not lead to skin sensitization reactions (RIFM, 1982b; RIFM, 1982a). Similarly, in a human maximization test, no sensitization reactions were observed when 2% or 1380 μg/cm^2 of phenylacetaldehyde dimethyl acetal in petrolatum was used for induction and challenge (RIFM, 1971). Additionally, in a confirmation of no induction in humans (CNIH) test with 1380 μg/cm^2 of phenylacetaldehyde dimethyl acetal in 95% ethanol, no reactions indicative of sensitization were observed in any of the 39 volunteers (RIFM, 1965).

Based on the weight of evidence from structural analysis and animal and human studies, phenylacetaldehyde dimethyl acetal does not present a concern for skin sensitization.

Additional References: Klecak (1979); Klecak (1985).

Literature Search and Risk Assessment Completed On: 10/07/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, phenylacetaldehyde dimethyl acetal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for phenylacetaldehyde dimethyl acetal in experimental models. UV/Vis absorption spectra indicate no absorption 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 the lack of absorbance, phenylacetaldehyde dimethyl acetal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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: 09/23/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for phenylacetaldehyde dimethyl acetal is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are limited inhalation data available on phenylacetaldehyde dimethyl acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.025 mg/day. This exposure is 56 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: UGCM, 1997

Literature Search and Risk Assessment Completed On: 10/13/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenylacetaldehyde dimethyl acetal 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, phenylacetaldehyde dimethyl acetal was identified as a fragrance material with the 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 phenylacetaldehyde dimethyl acetal 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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), phenylacetaldehyde dimethyl acetal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1993:** Biodegradation was assessed in a sealed vessel test based on OECD 301B guideline. Sealed bottles containing a mineral salts medium inoculated with filtered activated sludge plant secondary effluent and 10 mg/L of phenylacetaldehyde dimethyl acetal were incubated for 56 days. The biodegradation rate of phenylacetaldehyde dimethyl acetal was 56% after 56 days.

RIFM, 1994: Biodegradation was assessed using the sealed vessel test based on OECD Guideline 301B. Vessels containing mineral salt medium inoculated with activated sludge plant secondary effluent and 10 mg/L of phenylacetaldehyde dimethyl acetal were incubated for 28 days. Under the conditions of the test, biodegradation of 54.9% was observed after 28 days.

RIFM, 1999a: The inherent biodegradability of the test material was determined by the Respirometric Method according to the OECD 302C method. Mineral medium inoculated with fresh activated sludge and 30 mg/L of phenylacetaldehyde dimethyl acetal was stirred in a closed flask and incubated for up to 34 days. The biodegradation rate was 57% after 28 days and 59% after 34 days.

RIFM, 1998: Biodegradation was determined by the manometric respirometry test, according to the OECD 301F method. Mineral medium inoculated with fresh activated sludge and 100 mg/L of phenylacetaldehyde dimethyl acetal was stirred in a closed flask and incubated for 28 days. The biodegradation was 51% after 28 days.

RIFM, 1999c: The biodegradability of the test material was determined using the closed bottle test according to the OECD 301D guidelines. Under the conditions of the study, no biodegradation was observed.

RIFM, 2011: Ready biodegradability of the test material was evaluated using a manometric respirometry test according to the OECD 301F method. Biodegradation of 43% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. **RIFM, 1999c:** The *Daphnia magna* immobilization study was conducted according to the 92/69/EEC C.2 (1992) method under static conditions. The 48-h EC0 (arithmetic mean of analytical values) was >97.3 mg/L.

11.2.2.1.3. Other available data. Phenylacetaldehyde dimethyl acetal has been registered for REACH with the following additional data at this time (ECHA, 2017):

The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guidelines under static conditions. The 96-h LC50 value based on nominal test concentration was >100 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values, based on nominal test concentration for growth rate and yield, were reported to be 81.3 mg/L and 75.8 mg/L, respectively.

11.2.3. Risk assessment refinement

Since phenylacetaldehyde dimethyl acetal has passed the screening criteria, measured data are included for completeness only and have 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.23	2.23
Biodegradation Factor Used	0.1	0.1
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 6.452 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 09/29/21.

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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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 02/22/22.

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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	141.4			1000000	0.1414	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	157.6	88.94	64.52	10000	6.452	Neutral Organic SAR

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113226.

Appendix

Read-across Justification

Methods

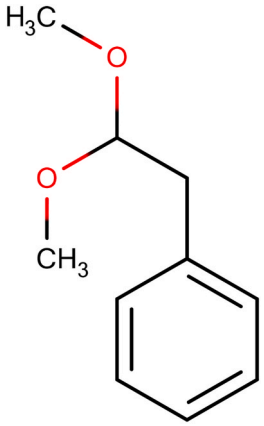
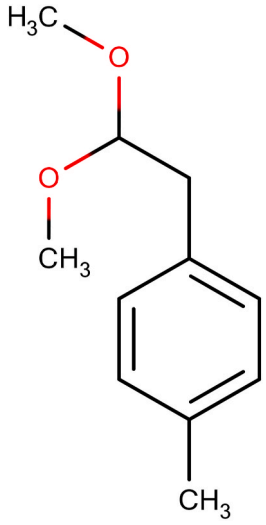
The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2018) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	WoE Material
Principal Name	Phenylacetaldehyde dimethyl acetal	*p*-(2,2-Dimethoxyethyl)toluene
CAS No.	101-48-4	42866-91-1
Structure		

(*continued on next page*)

(*continued*)

	Target Material	WoE Material
		
Similarity (Tanimoto Score)		0.91
SMILES	COC(Cc1ccccc1)OC	COC(Cc1ccc(C)cc1)OC
Endpoint		Genotoxicity (Mutagenicity)
Molecular Formula	$C_{10}H_{14}O_2$	$C_{11}H_{16}O_2$
Molecular Weight (g/mol)	166.22	180.247
Melting Point (°C, EPI Suite)	−0.08	17.22
Boiling Point (°C, EPI Suite)	219.76	238.29
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.77E+01	6.76E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.44E+03	4.20E+02
Log KOW	1.93	2.48
J_{max} (μg/cm^2/h, SAM)	18.89	9.34
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.49E-01	6.06E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
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

In silico evaluation was conducted to determine weight of evidence analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, *p*-(2,2-dimethoxyethyl)toluene (CAS # 42866-91-1) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- *p*-(2,2-Dimethoxyethyl)toluene (CAS # 42866-91-1) was used as a WoE material for the target material phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) for the genotoxicity endpoint.
  - o The target material and the WoE material are structurally similar and belong to the acetals group.
  - o The key difference between the target material and the WoE material is an additional methyl group at the para- position on the benzene ring in the WoE material compared to the target material. This structural difference is toxicologically insignificant.

- The similarity between the target material and the WoE material is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the WoE material are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the WoE material.
- Both the target material and the WoE material have an alert for Michael addition due to quinone and quinone-type chemicals. The predictions are superseded by data.
- The target material and the WoE material 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 WoE material and the target material.

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