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RIFM fragrance ingredient safety assessment, phenylpropionaldehyde dimethyl acetal, CAS Registry Number 90-87-9

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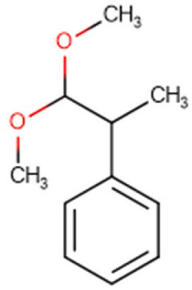
Name: 2-Phenylpropionaldehyde dimethyl acetal
CAS Registry Number: 90-87-9



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)
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.

2-Phenylpropionaldehyde dimethyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog *p*-(2,2-dimethoxyethyl)toluene (CAS # 42866-91-1) show that 2-phenylpropionaldehyde dimethyl acetal is not expected to be genotoxic. Data on analog phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) provide a calculated MOE >100 for the repeated dose and reproductive toxicity endpoints. Data and read-across to phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 2-phenylpropionaldehyde dimethyl acetal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). For the hazard assessment based on the screening data, 2-phenylpropionaldehyde dimethyl acetal is not PBT as per the IFRA Environmental Standards. For the risk assessment, 2-phenylpropionaldehyde dimethyl acetal was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

(*continued on next page*)

(*continued*)

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 2019; RIFM, 2016a)
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, 1982a; RIFM, 1982b; RIFM, 1965; RIFM, 1971; RIFM, 1975)
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: 42% (OECD 301 D)	RIFM (2020b)
Bioaccumulation: Screening-level: 16.45 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 120.6 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: 120.6 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1206 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** 2-Phenylpropionaldehyde dimethyl acetal
2. **CAS Registry Number:** 90-87-9
3. **Synonyms:** Benzene, (2,2-dimethoxy-1-methylethyl)-; 1,1-Dimethoxy-2-phenylpropane; Hydratropaldehyde dimethyl acetal; Hydratropic aldehyde dimethyl acetal; ヒドロアトロパアルデヒドジメチルアセタール; (2,2-Dimethoxy-1-methylethyl)benzene; Corps UA; Hydratropic ald DMA BHT; 2-Phenylpropionaldehyde dimethyl acetal
4. **Molecular Formula:** $C_{11}H_{16}O_2$
5. **Molecular Weight:** 180.24 g/mol
6. **RIFM Number:** 676
7. **Stereochemistry:** Stereoisomer not specified. One chiral center is present, and a total of 2 enantiomers are possible.

2. Physical data

1. **Boiling Point:** 227.23 °C (EPI Suite)
2. **Flash Point:** 182 °F; CC (Fragrance Materials Association [FMA] Database), 83 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.35 (EPI Suite)
4. **Melting Point**: 0.23 °C (EPI Suite)
5. **Water Solubility:** 542.5 mg/L (EPI Suite)
6. **Specific Gravity:** 0.992 (FMA Database)
7. **Vapor Pressure:** 0.0589 mm Hg at 20 °C (EPI Suite v4.0), 0.07 mm Hg at 20 °C (FMA Database), 0.0903 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:** Colorless to slightly yellow liquid with a powerful, earthy, warm, spicy, green, deep fruity odor, reminiscent of walnut, mushroom with a slightly floral-fruity undertone. Warm-earthy, distinctly mushroom taste in dilutions below 5 ppm. Higher concentrations are mostly nut-like, spicy, or sharp (Arctander, 1969).

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0054% (RIFM, 2020c)
2. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0087 mg/day (RIFM, 2020c)
3. **Total Systemic Exposure**:** 0.00033 mg/kg/day (RIFM, 2020c)

*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

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** *p*-(2,2-Dimethoxyethyl)toluene (CAS # 42866-91-1)
   b. **Repeated Dose Toxicity:** Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4)
   c. **Reproductive Toxicity:** Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4)
   d. **Skin Sensitization:** Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

2-Phenylpropionaldehyde dimethyl acetal 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.

9. REACH dossier

https://echa.europa.eu/registration-dossier/-/registered-dossier/31012/1/2 Available; accessed on 10/26/21 (ECHA, 2020).

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, 2-phenylpropionaldehyde dimethyl acetal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-phenylpropionaldehyde dimethyl acetal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-phenylpropionaldehyde dimethyl acetal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Increases in the mean number of revertant colonies were observed in strains TA100 and TA1535 in the absence of S9 (RIFM, 2019). For strain TA100, statistically significant increases in the frequency of revertant mutations were observed at 500, 1500, and 5000 μg/plate in the first study and 5000 μg/plate in the second study. However, all these increases were within the historical vehicle control range and therefore considered to be not biologically relevant. For strain TA1535, statistically significant increases in the frequency of revertant mutations were observed at 5000 μg/plate in the first study. While the increases were outside the historical vehicle control range, the increases were considered to be not biologically relevant due to a lack of evidence of a dose-response relationship and the lack of reproducibility in the second and third studies. Under the conditions of the study, 2-phenylpropionaldehyde dimethyl acetal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2-phenylpropionaldehyde dimethyl acetal; however, read-across can be made to *p*-(2,2-dimethoxyethyl)toluene (CAS # 42866-91-1; see Section VI).

The clastogenic activity of *p*-(2,2-dimethoxyethyl)toluene 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 *p*-(2,2-dimethoxyethyl)toluene in DMSO at concentrations up to 1000 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 850 μg/mL in the presence and absence of metabolic activation. *p*-(2,2-Dimethoxyethyl)toluene did induce binucleated cells with micronuclei when tested at 729 μg/mL in the 3-h treatment in the presence of an S9 activation system (RIFM, 2016a). However, the increases were within the historical control range and therefore considered to be not biologically relevant. Under the conditions of the study, *p*-(2,2-dimethoxyethyl)toluene was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-phenylpropionaldehyde dimethyl acetal.

Based on the data available, *p*-(2,2-dimethoxyethyl)toluene does not present a concern for genotoxic potential, and this can be extended to 2-phenylpropionaldehyde dimethyl acetal.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for 2-phenylpropionaldehyde dimethyl acetal is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-phenylpropionaldehyde dimethyl acetal. Read-across material phenylacetaldehyde dimethyl acetal (CAS # 101-48-4; see Section VI) has sufficient repeated dose toxicity data that can be used to support the repeated dose toxicity endpoint. An OECD 422/GLP-compliant 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 for 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) 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. For general systemic observations, treatment-related salivation was observed in both sexes (3 males and 2 females) in 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 at 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 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde dimethyl acetal, 200/0.00033 or 606061.

In addition, the total systemic exposure to 2-phenylpropionaldehyde dimethyl acetal (0.33 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.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for 2-phenylpropionaldehyde dimethyl acetal is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-phenylpropionaldehyde dimethyl acetal. Read-across material phenylacetaldehyde dimethyl acetal (CAS # 101-48-4; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD 422/GLP-compliant 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 for 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 test material-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 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde dimethyl acetal, 600/0.00033, or 1818182.

In addition, the total systemic exposure to 2-phenylpropionaldehyde dimethyl acetal (0.33 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 and read-across material phenylacetaldehyde dimethyl acetal (CAS # 101-48-4), 2-phenylpropionaldehyde dimethyl acetal does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-phenylpropionaldehyde dimethyl acetal. Based on the existing data and read-across material phenylacetaldehyde dimethyl acetal (CAS # 101-48-4; see Section VI), 2-phenylpropionaldehyde dimethyl acetal does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree v3.1.0). In a murine local lymph node assay (LLNA), read-across material phenylacetaldehyde dimethyl acetal was found to be non-sensitizing up to 100% (ECHA, 2017a; RIFM, 2016b). In 2 guinea pig maximization studies, the weight of evidence suggests that phenylacetaldehyde dimethyl acetal is not a sensitizer (RIFM, 1982a; RIFM, 1982b). In human maximization tests, no skin sensitization reactions were observed with 2-phenylpropionaldehyde dimethyl acetal or read-across material phenylacetaldehyde dimethyl acetal (RIFM, 1975; RIFM, 1971). Additionally, in a confirmation of no induction in humans (CNIH) test with 388 μg/cm^2 of read-across material 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, human study, and read-across material phenylacetaldehyde dimethyl acetal, 2-phenylpropionaldehyde 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, 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde 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, 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde dimethyl acetal is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-phenylpropionaldehyde dimethyl acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.0087 mg/day. This exposure is 160.9 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: None.

Literature Search and Risk Assessment Completed On: 10/18/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-phenylpropionaldehyde 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, 2-phenylpropionaldehyde dimethyl acetal 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) identified 2-phenylpropionaldehyde dimethyl acetal as possibly persistent but not 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), 2-phenylpropionaldehyde dimethyl acetal does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2020b**: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guideline. Biodegradation of 27% was observed after 28 days and 42% after 60 days.

11.2.2.1.2. Ecotoxicity. **RIFM, 2000**: The *Daphnia magna* acute immobilization test was conducted according to the OECD 201 guidelines under static conditions. The 48-h EC50 value based on the mean measured test concentration was reported to be > 95.1 mg/L.

11.2.2.1.3. Other available data. 2-Phenylpropionaldehyde dimethyl acetal has been registered for REACH with the following additional data available at this time (ECHA, 2020):

The *Daphnia magna* acute immobilization test was conducted according to the OECD 201 guidelines under static conditions. The 48-h EC50 value based on the mean measured test concentration was reported to be > 100 mg/L.

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

11.2.3. Risk assessment refinement

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	2.35	2.35
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1206 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	120.6			1000000	0.1206	

- **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 02/23/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113155.

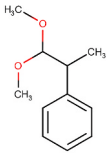
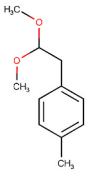
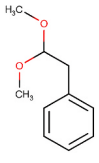
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with 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, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- 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 (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 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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Read-across Material	Read-across Material
Principal Name	2-Phenylpropionaldehyde dimethyl acetal	*p*-(2,2-Dimethoxyethyl)toluene	Phenylacetaldehyde dimethyl acetal
CAS No.	90-87-9	42866-91-1	101-48-4
Structure			
Similarity (Tanimoto Score)		0.82	0.89
SMILES	COC(OC)C(C)c1ccccc1	COC(Cc1ccc(C)cc1)OC	COC(Cc1ccccc1)OC
Endpoint		Genotoxicity	Skin sensitization Repeated dose toxicity Reproductive toxicity

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Molecular Formula	$C_{11}H_{16}O_2$	$C_{11}H_{16}O_2$	$C_{10}H_{14}O_2$
Molecular Weight (g/mol)	180.247	180.247	166.22
Melting Point (°C, EPI Suite)	0.23	17.22	−0.08
Boiling Point (°C, EPI Suite)	227.23	238.29	219.76
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.20E+01	6.76E+00	1.77E+01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	5.43E+02	4.20E+02	1.44E+03
Log K_{OW}	2.35	2.48	2.3[1]
J_{max} (μg/cm^2/h, SAM)	9.83	9.34	18.89
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.30E-01	6.06E-01	5.49E-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	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Toluene (Renal toxicity) Alert		Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group		Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)		Toxicant (good 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 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 skin sensitization reactivity domain alerts were identified.		No skin sensitization reactivity domain alerts were identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

1. RIFM, 1999.

Summary

There is insufficient toxicity data on 2-phenylpropionaldehyde dimethyl acetal (CAS # 90-87-9). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) and *p*-(2,2-dimethoxyethyl)toluene (CAS # 42866-91-1) were identified as read-across analogs with data for their respective toxicity endpoints.

Conclusion

- *p*-(2,2-Dimethoxyethyl)toluene (CAS # 42866-91-1) was being used as a structurally similar read-across analog for target material 2-phenylpropionaldehyde dimethyl acetal (CAS # 90-87-9) for the clastogenicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aryl acetals.
  - o The target material and the read-across analog have the phenylacetaldehyde dimethyl acetal structure in common.
  - o The key difference between the target material and the read-across analog is that the target has an additional methyl substitution on the phenethyl fragment, while the read-across analog lacks such a substitution. In addition, the read across material has a para-methyl group which the target material lacks.
  - o The target material and the read-across analog have Tanimoto scores, as mentioned in the above table. The Tanimoto score is mainly driven by the phenylacetaldehyde dimethyl acetal structure fragment. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.

- The similarity between the target material and the read-across analog is indicated by the Tanimoto scores. Differences between the structures that affect the Tanimoto scores are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the QSAR OECD Toolbox, structural alerts for the skin sensitization endpoint are consistent between the target material and the read-across analog.
- The target material and the read-across analog have an alert of reactivity through quinone-type materials via P450 mediated metabolism. Based on expert judgement, it is concluded that the structural alert is for the minor metabolic pathway and thus, is expected to be relatively insignificant. The data on the read-across analog further confirm that the substance does not pose a concern for genotoxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read-across analog and the target material.
- The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

- Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) could be used as a structurally similar read-across analog for target material 2-phenylpropionaldehyde dimethyl acetal (CAS # 90-87-9) for the skin sensitization, repeated dose toxicity, and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of aryl acetals.
  - The target material and the read-across analog have phenylacetaldehyde dimethyl acetal structure in common.
  - The key difference between the target material and the read-across analog is that the target material has an additional methyl substitution on the ethyl portion of the phenethyl fragment, while the read-across analog lacks such a substitution.
  - The target material and the read-across analog have Tanimoto scores, as mentioned in the above table. The Tanimoto score is mainly driven by the phenylacetaldehyde dimethyl acetal structure fragment. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox, structural alerts for the skin sensitization endpoint are consistent between the target material and the read-across analog.
  - According to the CAESAR model, both the read-across analog and the target material are predicted to be sensitizers. Data described above in the skin sensitization section show that the read-across material does not present a concern for skin sensitization. Therefore, the prediction will be superseded by the data.
  - The read-across analog was alerted as styrene-related renal toxicity by OECD QSAR Toolbox v4.2 according to the HESS categorization and a toxicant by the CAESAR model for developmental toxicity. The read-across material and the target material both were alerted as toluene-related renal toxicity by OECD QSAR Toolbox v4.2 according to the HESS categorization. The data on the read-across analog confirm that the MOE is adequate at the current levels of use. Based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

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