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Short Review

RIFM fragrance ingredient safety assessment, 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate, CAS Registry Number 68844-96-2

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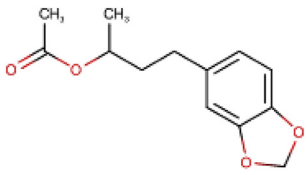
Version: 032178. This version replaces any previous versions.



Name: 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate
CAS Registry Number: 68844-96-2

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America

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NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WOE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

Summary: The use of this material under current conditions is supported by existing information.

1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate is not genotoxic. Data on the read-across analog piperonyl acetate (CAS# 326-61-4) show that 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not have skin sensitization potential. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate 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, 2016a; RIFM, 2016b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization (RIFM, 2015)
Phototoxicity/ Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.62 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 101 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 14.57 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) (RIFM Framework; Salvito et al, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 14.57 mg/L (RIFM Framework; Salvito et al, 2002))
RIFM PNEC is: 0.01457 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate
2. **CAS Registry Number:** 68844-96-2
3. **Synonyms:** 1,3-Benzodioxole-5-propanol,.α.-methyl-, acetate; 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate
4. **Molecular Formula:** $C_{13}H_{16}O_4$
5. **Molecular Weight:** 236.27
6. **RIFM Number:** 7037
7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 319.83 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}**: 3.54 (EPI Suite)
4. **Melting Point**: 87.8 °C (EPI Suite)
5. **Water Solubility:** 26.55 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.000169 mm Hg @ 25 °C (EPI Suite), 0.0000866 mm Hg @ 20 °C (EPI Suite 4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a strong odor.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00053% (RIFM, 2016c)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or 0.0000024 mg/day (RIFM, 2016c)
4. **Total Systemic Exposure**:** 0.0000053 mg/kg/day (RIFM, 2016c)

*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**: Piperonyl acetate (CAS # 326-61-4)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification:** See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate is not reported to occur in food 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

pre-registered for 11/30/2010; no dossier available as of 03/21/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). The mutagenic activity of 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate was not mutagenic in the Ames test.

The clastogenic activity of 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016b). Under the conditions of the study, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate or any read-across materials. The total systemic exposure to 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate (0.005 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: 07/25/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate or any read-across materials. The total systemic exposure to 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate (0.005 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) (Kroes et al., 2007) 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: 07/25/17.

10.1.4. Skin sensitization

Based on the read-across piperonyl acetate (CAS # 326-61-4), 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate. Based on the read-across analog piperonyl acetate (CAS # 326-61-4; see Section V), 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a concern for skin sensitization. The chemical structures of these materials indicate that 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate would not be expected to react with skin proteins, but read-across piperonyl acetate would be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). However, in a confirmatory human repeat insult patch test (HRIPT) with 4724 μg/cm2 of read-across piperonyl acetate, no reactions indicative of sensitization were observed in any of the 104 volunteers (RIFM, 2015). Additionally, in an HRIPT with 37 subjects, no reactions to 194 μg/cm2 piperonyl acetate were observed (RIFM, 1964). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm2 read-across material piperonyl acetate (RIFM, 1973). Based on the weight of evidence from structural analysis and read-across analog piperonyl acetate, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/02/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009; Henry et al., 2009). Based on lack of absorbance, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate 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: 07/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0000024 mg/day. This exposure is 195833 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: 08/02/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate 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.

10.2.2. Risk assessment

Based on the current volume of use (2015), 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	14.57			1,000,000	0.01457	

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

Exposure	Europe	North America
Log K_{ow} Used	3.5	3.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 2
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 0.01457 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 7/31/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.07.006.

Appendix

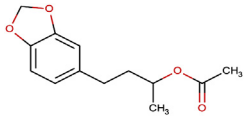
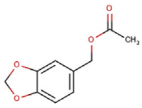
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment

(OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material
Principal Name	1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate	Piperonyl acetate
CAS No.	68844-96-2	326-61-4
Structure		
Similarity (Tanimoto Score)		0.78
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_{13}H_{16}O_4$	$C_{10}H_{10}O_4$
Molecular Weight	236.27	194.19
Melting Point (°C, EPI Suite)	87.80	68.01
Boiling Point (°C, EPI Suite)	319.83	285.09
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.0225	0.226
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.54	2.14
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	26.55	692.8
J_{max} (mg/cm^2/h, SAM)	5.977	15.858
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.85E-008	1.65E-008
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	•SN2 reaction
Protein Binding (OECD)	• SN2 reaction	•SN2 reaction
Protein Binding Potency	• Not possible to classify	•Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	•SN2 reaction
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	•No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate (CAS # 68844-96-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, piperonyl acetate (CAS # 326-61-4) was identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Piperonyl acetate (CAS # 326-61-4) was used as a read-across analog for the target material 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate (CAS # 68844-96-2) for the skin sensitization endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of esters.
  - ○ The target substance and the read-across analog share a common 1,3-benzodioxole fragment on alcohol portion of ester.
  - ○ The key difference between the target substance and the read-across analog is that the target has a longer alcohol chain portion compared to the read-across. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the 1,3-benzodioxole fragment on the alcohol portion of the ester. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.

- Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- The read-across analog is predicted to have positive protein binding alerts by the OASIS and OECD models and the target material is predicted to have protein binding alerts by the OECD model for skin sensitization. All the other alerts for skin sensitization were predicted to be negative. According to these predictions, the read-across analog is expected to be more reactive compared to the target substance. Data superseded predictions in this case.
- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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