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Short Review

RIFM fragrance ingredient safety assessment, propanal diethyl acetal, CAS registry number 4744-08-5

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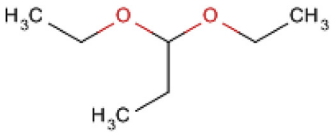
ABSTRACT

There are insufficient toxicity data on the target material propanal diethyl acetal (CAS # 4744-08-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs acetal (CAS # 105-57-7) and butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3) were identified as read-across materials with sufficient data for toxicological evaluation of genotoxicity.

Version: 050318. This version replaces any previous versions.
Name: Propanal diethyl acetal
CAS Registry Number: 4744-08-5



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.,

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2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.
Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM 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.
Propanal diethyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analogs acetal (CAS # 105-57-7) and butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3) show that propanal diethyl acetal is not expected to be genotoxic. Based on the existing data and the application of the non-reactive DST, propanal diethyl acetal does not present a concern for skin sensitization. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; propanal diethyl acetal was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients (i.e., PEC/PNEC) could not be calculated due to no volume of use reported in North America and Europe.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(REACH Dossier; RIFM, 2017)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: No safety concerns at current declared use levels; Exposure is below DST.	
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: 2.9 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 6.7 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Not applicable	
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe): No volume of use reported for North America or Europe	
Critical Ecotoxicity Endpoint: Not Applicable	
RIFM PNEC: Not Applicable.	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable	

1. Identification

1. **Chemical Name:** Propanal diethyl acetal
2. **CAS Registry Number:** 4744-08-5
3. **Synonyms:** 1,1-Diethoxypropane; Propane, 1,1-diethoxy-; Propionaldehyde diethyl acetal; Propanal diethyl acetal
4. **Molecular Formula:** $C_7H_{16}O_2$
5. **Molecular Weight:** 132.2
6. **RIFM Number:** 6772

2. Physical data

1. **Boiling Point:** 130.82 °C (EPI Suite)
2. **Flash Point:** 55.00 °F; TCC (12.78 °C)*
3. **Log K_{OW}**: 1.7 (EPI Suite)
4. **Melting Point**: 56.16 °C (EPI Suite)
5. **Water Solubility:** 3209 mg/L (EPI Suite)
6. **Specific Gravity:** 0.82400 to 0.83000 @ 25.00 °C*
7. **Vapor Pressure:** 12.5 mm Hg @ 20 °C (EPI Suite v4.0), 16.5 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} $\cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid*

*http://www.thegoodscentscompany.com/data/rw1278981.html, retrieved 02/09/2017.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Shower gel products:** 0.00020% (RIFM, 2015)
   (No reported use in Hydroalcoholics)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or 0.00000010 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.0000013 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2017; Safford et al., 2015, 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 I, Low

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

2. Anpalogs Selected:
   a. **Genotoxicity:** Acetal (CAS # 105-57-7); Butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Propanal diethyl acetal is reported to occur in the following foods by the VCF*:

Apple brandy (Calvados)
Apple processed (*Malus* species)
Arrack
Grape brandy
Milk and milk products
Passion fruit (*Passiflora* species)
Pear brandy
Plum brandy
Raspberry, blackberry, and boysenberry
Rum
Sherry
Strawberry (*Fragaria* species)
Whisky
Wine

*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 2010, no dossier available as of 05/03/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, propanal diethyl acetal does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Propanal diethyl acetal was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenic activity of propanal diethyl acetal; however, read-across can be made to butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3; see Section 5). The mutagenic activity of butane, 1,1'-[methylenebis(oxy)]bis-has been evaluated in multiple bacterial reverse mutation assays conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with butane, 1,1'-[methylenebis(oxy)]bis-in water at concentrations up to 10000 μg/plate. Statistically significant increases in the mean number of revertant colonies of TA98 and TA100 strains were observed in absence of metabolic activation with 3.9- and 2.1-fold increases, respectively. No increases in the mean number of revertant colonies were observed at any tested dose in the presence of S9. In another bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA102, and *Escherichia coli* strain WP2uvrA were treated with butane, 1,1'-[methylenebis(oxy)]bis-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 of S9. In another bacterial reverse mutation assay *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with butane, 1,1'-[methylenebis(oxy)]bis-at concentrations up to 2500 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence of S9. A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster ovary cells were treated for 4 h with butane, 1,1'-[methylenebis(oxy)]bis-in sterile deionized water at concentrations up to 5 mg/mL. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any dose of the test item, either with or without metabolic activation (REACH Dossier). Taken together—2 negative results and one positive result in the bacterial reverse mutation assay and a negative result in the mammalian cell gene mutation study—we can conclude that butane, 1,1'-[methylenebis(oxy)]bis-is not considered to be mutagenic, and this can be extended to propanal diethyl acetal.

There are no studies assessing the clastogenic activity of propanal diethyl acetal; however, read-across can be made to acetal (CAS # 105-57-7; see Section 5). The clastogenic activity of 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 for 3 and 24 h with acetal in dimethyl sulfoxide (DMSO) at concentrations up to 1182 μg/mL in the presence and absence of S9 metabolic activation. A statistically significant increase in the frequency of micronucleated binucleate cells (MNBN) was observed at the highest evaluated concentration (1005 μg/mL) in the approximate 24-h treatment without S9. The percent MNBN frequency (1.15%) at this concentration was outside the 95% reference range

Table 1
Acceptable concentrations for propanal diethyl acetal based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.00%
2	Products applied to the axillae	0.021%	0.00%
3	Products applied to the face using fingertips	0.41%	0.00%
4	Fine fragrance products	0.39%	0.00%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%
10	Household care products with mostly hand contact	2.70%	0.00%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00%

Note.
[a]For a description of the categories, refer to the IFRA/RIFM Information Booklet (www.rifm.org/doc).
[b]Negligible exposure (< 0.01%).

(0.10–1.10) but was within the observed historical control range (0.00–1.20%) for this treatment condition in male donors. Additionally, no dose response was observed. Therefore, the results were considered of questionable biological relevance. No significant increases in the MNBN frequencies were observed at any evaluated concentration in the 3-h treatments with or without S9. To confirm this questionable finding, a confirmatory assay was conducted in the 24-h arm of the study without metabolic activation. No significant increases in the MNBN frequency were observed at any evaluated concentration in the confirmatory assay. Considering the questionable relevance of the observed increase in the initial assay along with the increase being non-reproducible in the confirmatory study, these effects were was considered as biologically non-relevant. Taken together, acetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017). Under the conditions of the study, acetal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to propanal diethyl acetal.

Based on the data available on read-across materials, propanal diethyl acetal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/26/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on propanal diethyl acetal or any read-across materials. The total systemic exposure to propanal diethyl acetal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on propanal diethyl acetal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to propanal diethyl acetal (0.0013 μg/kg/day) is below the TTC (30 μg/kg/day) 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: 05/24/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on propanal diethyl acetal or any read-across materials. The total systemic exposure to propanal diethyl acetal is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on propanal diethyl acetal or any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to propanal diethyl acetal (0.0013 μg/kg/day) is below the TTC (30 μg/kg/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/24/2017.

10.1.4. Skin sensitization

Based on the existing data and application of DST, propanal diethyl acetal does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for propanal diethyl acetal. However, in a human repeated insult patch test, no skin sensitization reactions were observed (RIFM, 1975). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentrations for propanal diethyl acetal, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/26/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, propanal diethyl acetal would not be expected to present a concern for phototoxicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for propanal diethyl acetal in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity

(Henry et al., 2009). Based on lack of absorbance, propanal diethyl acetal does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level of propanal diethyl acetal is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on propanal diethyl acetal. Based on the Creme RIFM model, the inhalation exposure is 0.00000010 mg/day. This exposure is 14000000 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: 1/27/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of propanal diethyl 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, propanal diethyl acetal was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2011 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.1 did not identify propanal diethyl acetal as either being possibly persistent nor 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Not applicable.

10.2.2. Biodegradation

No data available.

10.2.3. Ecotoxicity

No data available.

10.2.4. Other available data

No data available.

10.2.5. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 02/09/2017.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.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.

Declaration of interests

- 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.

- The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110588.

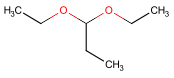
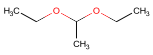
Appendix

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.

- 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 v4.1 (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, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- 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, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target material	Read-across materials	
Principal Name	Propanal diethyl acetal	Acetal	Butane, 1,1'-[methylenebis(oxy)] bis-
CAS No.	4744-08-5	105-57-7	2568-90-3
Structure			
Similarity (Tanimoto score)		0.93	0.78
Read-across endpoint		• Genotoxicity	• Genotoxicity
Molecular Formula	$C_7H_{16}O_2$	$C_6H_{14}O_2$	$C_9H_{20}O_2$
Molecular Weight	132.2	118.18	160.26
Melting Point (°C, EPI Suite)	−56.16	−68.60	−20.93
Boiling Point (°C, EPI Suite)	130.82	107.53	187.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.21E+003	5.26E+003	183
Log Kow (KOWWIN v1.68 in EPI Suite)	1.7	0.84	2.75
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3209	44000	304.9
J_{max} (μg/cm^2/h, SAM)	256.255	328.632	15.78
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.57E-004	1.18E-004	2.77E-004
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• No alert found	• No alert found	• No alert found
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• No alert found	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified	• Not classified
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	No metabolites	See Supplemental Data 1	See Supplemental Data 2

12. Conclusions

- The following materials were used as structurally similar read-across analogs for the target material, propanal diethyl acetal (CAS # 4744-08-5): acetal (CAS # 105-57-7) and butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3) for the genotoxicity endpoint
  - o The target substance and the read-across analogs are structurally similar and belong to the structural class of aliphatic acetals.
  - o The target substance and the read-across analogs share the acetal functional group with saturated aliphatic alkyl chain substituents.

- o The key difference between the target substance and the read-across analogs is that the target substance has longer saturated aliphatic chain substituents on the acetal compared to the read-across analogs. The differences in structure between the target substance and the read-across analogs do not raise additional structural alerts, so the structural differences are not relevant from a toxicological endpoint perspective.
- o Similarity between the target substance and the read-across analogs is indicated by the Tanimoto scores provided in the above table. The Tanimoto score is mainly driven by the acetal functional group with the dimethyl groups. The differences in the structure that are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
- o The target substance and the read-across analogs have similar physical–chemical properties. Differences in some of the physical–chemical properties of the target substance and the read-across analogs are estimated to be toxicologically insignificant for the genotoxicity endpoint.
- o Structural alerts for the genotoxicity endpoint are consistent between the target substance and their respective read-across analog as seen in the table above.
- o The target substance is predicted to have no metabolites, while the read-across analogs acetal and butane, 1,1'-[methylenebis(oxy)]bis-are expected to be metabolized similarly as shown by the metabolism simulator.
- o The structural alerts for genotoxicity are consistent between the metabolites of the read-across analogs acetal and butane, 1,1'-[methylenebis (oxy)]bis-.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2011. Volume of Use Survey, 2011.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox. v4.2. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1975. Repeated Insult Patch Test with Propanal Diethyl Acetal (Propionaldehyde Diethyl Acetal) in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 54778. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Report on the Testing of Propanal Diethyl Acetal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 67435. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. Exposure Survey 06, February 2015.

RIFM (Research Institute for Fragrance Materials, Inc), 2017. Acetal: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 71499. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.