Food and Chemical Toxicology 122 (2018) S445–S452

Contents lists available at ScienceDirect

Food and Chemical Toxicology

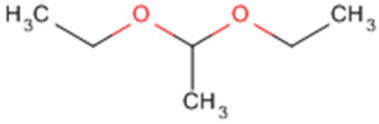
journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, acetal, CAS Registry Number 105-57-7

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

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

Version: 050418. This version replaces any previous versions.
Name: Acetal
CAS Registry Number: 105-57-7



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

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

https://doi.org/10.1016/j.fct.2018.09.077
Received 7 May 2018; Received in revised form 29 August 2018; Accepted 28 September 2018
Available online 01 October 2018
0278-6915/

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 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.

Acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from acetal and the read-across analog butane, 1,1'-[methylenebis(oxy)] bis- (CAS# 2568-90-3) show that acetal is not genotoxic. Based on the existing data and application of the non-reactive DST, acetal does not present a concern for skin sensitization. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated 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; acetal 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. (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 the 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: 3.16 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1067 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: 1067 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC: 1.067 µg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level.

1. Identification

1. **Chemical Name:** Acetal
2. **CAS Registry Number:** 105-57-7
3. **Synonyms:** Acetaldehyde, diethyl acetal; 1,1-Diethoxyethane; Diethyl acetal; Ethane, 1,1-diethoxy-; Ethylidine diethyl ether; ｱｾﾄｱﾙﾃﾞﾋﾄﾞｼﾞｱﾙｷﾙ(C = 1 ~ 6)ｱｾﾀｰﾙ; Acetal
4. **Molecular Formula:** $C_6H_{14}O_2$
5. **Molecular Weight:** 118.18
6. **RIFM Number:** 481

2. Physical data

1. **Boiling Point:** 102 °C (FMA), 107.53 °C (EPI Suite)
2. **Flash Point:** 20 °C (GHS), < 40 °F; CC (FMA)
3. **Log K_{ow}:** 0.84 (Abraham and Rafols, 1995), 1.2 (EPI Suite)
4. **Melting Point**: 68.6 °C (EPI Suite)
5. **Water Solubility:** 19540 mg/L (EPI Suite)
6. **Specific Gravity:** 0.831 (FMA)
7. **Vapor Pressure:** 30.5 mm Hg @ 20 °C (EPI Suite v4.0), 21 mm Hg 20 °C (FMA), 39.4 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} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless, volatile liquid with fruity-green odor and nutty aftertaste

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0030% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.000062 mg/kg/day or 0.0045 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00046 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; 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 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; 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 I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** 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

RIFM, 1962: The degree of conversion of acetal to aldehyde was determined in the following study. Fifty–mL portions of either simulated gastric juice or intestinal fluid were incubated with 1 mmol of acetal at 37 °C for up to 5 h. Following the incubation, each medium was analyzed for aldehyde content by the hydroxylamine hydrochloride method. The degree of hydrolysis in the gastric juice was 92.3%, 92.4%, 89.6%, 91.7%, 90.0% at 1, 2, 3, 4, and 5 h, respectively. The degree of hydrolysis in the intestinal fluids was 5.4%, 8.9%, 6.8%, 8.0%, 9.7% at 1, 2, 3, 4, and 5 h, respectively.

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

Acetal is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Anise brandy.
Apple brandy (Calvados).
Apple processed (*Malus* species).
Arrack.
Bantu beer.
Beer.
Blackberry brandy.
Cherry brandy.
Chicken.
Chinese liquor (baijiu).
Chinese quince (*Pseudocydonia sinensis* Schneid).
Cider (apple wine).
Citrus fruits.
Cocoa.
Durian (*Durio zibethinus*).
Elderberry (*Sambucus nigra* L.).
Grape (*Vitis* species).
Grape brandy.
Guava and feyoa.
Guava wine.
Honey.
Mangifera species.
Milk and milk products.
Muruci (*Byrsonima crassifolia*).

Mustard (*Brassica* species).
Papaya (*Carica papaya* L.).
Passion fruit (*Passiflora* species).
Passion fruit wine.
Pear brandy.
Peas (*Pisum sativum* L.)
Plum (*Prunus* species).
Plum brandy.
Plum wine.
Pork.
Potato (*Solanum tuberosum* L.).
Prickly pear (*Opuntia ficus indica*).
Radish (*Raphanus sativus* L.)
Raspberry, blackberry, and boysenberry.
Rum.
Sauerkraut.
Sherry.
Shoyu (fermented soya hydrolysate).
Soursop (*Annona muricata* L.)
Strawberry (*Fragaria* species).
Sugar molasses.
Syzygium species.
Tequila (*Agave tequilana*).
Vanilla.
Vinegar.
Wheaten bread.
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 that contains information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA STANDARD

None.

9. REACH dossier

Available; accessed 09/01/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Acetal was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 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 the 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 was conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary were treated with butane, 1,1'-[methylenebis(oxy)]bis-in sterile deionized water at concentrations up to 5 mg/mL for 4 h. 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 1 positive result in the bacterial reverse mutation assay and a negative result in the mammalian cell gene mutation study, it can be concluded that butane, 1,1'-[methylenebis(oxy)]bis-is not considered to be mutagenic, and this can be extended to acetal.

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 (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.

Based on the data available, 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 acetal or any read-across materials. The total systemic exposure to 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 acetal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to acetal (0.46 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 acetal or any read-across materials. The total systemic exposure to 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 acetal or any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to acetal (0.46 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, acetal does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig open epicutaneous test, acetal was reported to be negative at 10% (Klecak, 1985). Similarly, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1974). 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 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: 01/26/17.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 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, 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 for 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 acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.0045 mg/day. This exposure is 311 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: Carpenter et al., 1949; Smyth et al., 1949.

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 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

Table 1
Acceptable concentrations for 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%[b]
2	Products applied to the axillae	0.021%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.000%[b]
6	Products with oral and lip exposure	0.23%	0.01%
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%	0.01%
10	Household care products with mostly hand contact	2.70%	0.05%
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	0.29%

Notes.

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet. (www.rifm.org/doc).

[b] Negligible exposure (< 0.01%).

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, 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 v4.1 (US EPA, 2012a) did not identify 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), acetal 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. Acetal has been registered under 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.05	1.05
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 1.067 µg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 02/07/2017.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	<u>1067</u>			1,000,000	1.067	

*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 to this article can be found online at https://doi.org/10.1016/j.fct.2018.09.077.

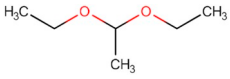
Appendix

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 were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, 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	Acetal	Butane, 1,1'-[methylenebis(oxy)] bis-
CAS No.	105-57-7	2568-90-3
Structure		
Similarity (Tanimoto score)		0.72
Read-across endpoint		• Genotoxicity
Molecular Formula	$C_6H_{14}O_2$	$C_9H_{20}O_2$
Molecular Weight	118.18	160.26
Melting Point (°C, EPI Suite)	−68.60	−20.93
Boiling Point (°C, EPI Suite)	107.53	187.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.26E+003	183
Log Kow (KOWWIN v1.68 in EPI Suite)	0.84	2.75
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	44000	304.9
J_{max} (mg/cm^2/h, SAM)	328.632	15.78
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.18E-004	2.77E-004
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• 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
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on the target material acetal (CAS # 105-57-7). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment,

read-across analog butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- The following material was used as structurally similar read-across analog for the target material acetal (CAS # 105-57-7) for the genotoxicity endpoint: butane, 1,1'-[methylenebis(oxy)]bis- (CAS # 2568-90-3).
  - ○ The target substance and the read-across analog are structurally similar and belong to the structural class of aliphatic acetals.
  - ○ The target substance and the read-across analog have an acetal functional group common among them.
  - ○ The key difference between the target substance and the read-across analog is that they have different lengths of alkyl chains on the alcohol portion. The target substance has a methyl substitution on the aldehyde portion, which the read-across analog lacks, and the read-across analog has a longer aliphatic chain compared to the target. The differences in structure between the target substance and the read-across analog do not raise additional structural alerts, so the structural differences are not relevant from a toxicological endpoint perspective.
  - ○ Similarity between the target substance and the read-across analog is indicated by a Tanimoto score provided in the above table. The Tanimoto score is mainly driven by the acetal group and the aliphatic chain on the alcohol portion. The differences in the structure that are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
  - ○ The target substance and the read-across analog have similar physical–chemical properties. The J_{max} value of the target and the read-across analogs appear to be different. But with the calculated J_{max}, both the read-across analog substance as well as the target substance are predicted to have skin absorption at 80%. Other differences in the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for genotoxicity, developmental, or repeated dose toxicity endpoints.
  - ○ According to the QSAR OECD Toolbox (v3.4), structural alerts for genotoxicity are consistent between the target substance and the read-across analog as seen in the table above.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - ○ The structural alerts for toxicological endpoints are consistent between the metabolites of the read-across analog and the target substance.
  - ○ The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.

XII. References

Abraham, M.H., Rafols, C., 1995. Factors that influence tadpole narcosis. An LFER analysis. J. Chem. Soc. Perkin Trans. 2 (10), 1843–1851.

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.

Carpenter, C.P., Smyth Jr., H.F., Pozzani, U.C., 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31 (6), 343–346 The Journal of Industrial Hygiene and Toxicology.

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/.

ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

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.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14. pp. 152–171.

OECD, 2012. The OECD QSAR Toolbox, v 3.4. Retrieved from. http://www.qsartoolbox.org/.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1962. In Vitro Digestion of Four Acetals. Private Communication to FEMA. Unpublished Report from Morgareidge, K. RIFM Report Number 24543. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1801. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of Acetal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65503. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. Exposure Survey 07, May 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.

Smyth, H.F., Carpenter, C.P., Weil, C.S., 1949. Range-finding toxicity data, list III. The journal of industrial hygiene and toxicolology. J. Ind. Hyg. Toxicol. 31 (1), 60–63.

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.