

## Short review

## RIFM fragrance ingredient safety assessment, decanal dimethyl acetal, CAS Registry Number 7779-41-1



A.M. Api<sup>a,\*</sup>, D. Belsito<sup>b</sup>, D. Botelho<sup>a</sup>, D. Browne<sup>a</sup>, M. Bruze<sup>c</sup>, G.A. Burton Jr.<sup>d</sup>, J. Buschmann<sup>e</sup>, M.L. Dagli<sup>f</sup>, M. Date<sup>a</sup>, W. Dekant<sup>g</sup>, C. Deodhar<sup>a</sup>, M. Francis<sup>a</sup>, A.D. Fryer<sup>h</sup>, K. Joshi<sup>a</sup>, S. La Cava<sup>a</sup>, A. Lapczynski<sup>a</sup>, D.C. Liebler<sup>i</sup>, D. O'Brien<sup>a</sup>, R. Parakhia<sup>a</sup>, A. Patel<sup>a</sup>, T.M. Penning<sup>j</sup>, G. Ritacco<sup>a</sup>, J. Romine<sup>a</sup>, D. Salvito<sup>a</sup>, T.W. Schultz<sup>k</sup>, I.G. Sipes<sup>l</sup>, Y. Thakkar<sup>a</sup>, E.H. Theophilus<sup>a</sup>, A.K. Tiethof<sup>a</sup>, Y. Tokura<sup>m</sup>, S. Tsang<sup>a</sup>, J. Wahler<sup>a</sup>

<sup>a</sup> Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA

<sup>b</sup> Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA

<sup>c</sup> Member RIFM Expert Panel, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgratan 101, Entrance 47, Malmö SE-20502, Sweden

<sup>d</sup> Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 48109, USA

<sup>e</sup> Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany

<sup>f</sup> 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

<sup>g</sup> Member RIFM Expert Panel, University of Würzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany

<sup>h</sup> Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA

<sup>i</sup> 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

<sup>j</sup> 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

<sup>k</sup> Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA

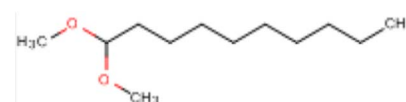
<sup>l</sup> Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA

<sup>m</sup> 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: 100617. This version replaces any previous versions.**

**Name:** Decanal dimethyl acetal

**CAS Registry Number:** 7779-41-1



**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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 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

\* Corresponding author.

E-mail address: [A.Api@rifm.org](mailto:A.Api@rifm.org) (A.M. Api).

**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  
**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  
**RIFM** - Research Institute for Fragrance Materials  
**RQ** - Risk Quotient  
**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** - Ultra Violet/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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 guidance relevant to human health and environmental protection.

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

Decanal dimethyl acetal was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog octanal dimethyl acetal (CAS # 10022-28-3) show that decanal dimethyl acetal is not expected to be genotoxic. The skin sensitization endpoint was completed using DST for non-reactive (900  $\mu\text{g}/\text{cm}^2/\text{day}$ ); exposure is below the DST. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material; the exposure to decanal dimethyl acetal is below the TTC (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; decanal dimethyl acetal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, decanal dimethyl 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. (RIFM, 2014a; RIFM, 2014b)  
**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: 3.03 (Biowin 3) (US EPA, 2012a)  
**Bioaccumulation:** Screening-Level: 10.7 L/kg (US EPA, 2012a)  
**Ecotoxicity:** Screening-Level: Fish LC50: 4.065 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: 4.065 mg/L (RIFM Framework; Salvito et al., 2002)  
**RIFM PNEC is:** 0.004065  $\mu\text{g}/\text{L}$   
**• Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not applicable; cleared at screening-level.

## 1. Identification

- Chemical Name:** Decanal dimethyl acetal
- CAS Registry Number:** 7779-41-1
- Synonyms:** Capraldehyde dimethyl acetal; Decane, 1,1-dimethoxy-; Decylaldehyde dimethyl acetal; 1,1-Dimethoxydecane; Decanal dimethyl acetal
- Molecular Formula:** C<sub>12</sub>H<sub>26</sub>O<sub>2</sub>
- Molecular Weight:** 202.34
- RIFM Number:** 887

## 2. Physical data

- Boiling Point:** 78 °C 1 mm Hg [FMA Database], 233.71 °C [US EPA, 2012a]
- Flash Point:** > 200 °F; CC [FMA Database], > 93 °C [GHS Database]
- Log K<sub>ow</sub>:** 4.15 [US EPA, 2012a]
- Melting Point:** 2.05 °C [US EPA, 2012a]
- Water Solubility:** 12.12 mg/L [US EPA, 2012a]
- Specific Gravity:** 0.824 [FMA Database]
- Vapor Pressure:** 0.0662 mm Hg @ 20 °C [US EPA, 2012a], 0.02 mm Hg 20 °C [FMA Database], 0.1 mm Hg @ 25 °C [US EPA, 2012a]
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol<sup>-1</sup> · cm<sup>-1</sup>)
- Appearance/Organoleptic:** Colorless liquid with a green-fruity, citrus-waxy odor.

## 3. Exposure

- Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2011)
- 95th Percentile Concentration in Roll on Deodorants**  
(no reported use in Hydroalcoholics): 0.0018% (RIFM, 2015).
- Inhalation Exposure\*:** 0.000012 mg/kg/day or 0.000086 mg/day (RIFM, 2015)
- Total Systemic Exposure\*\*:** 0.00023 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, 2017; 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, 2017; Comiskey et al., 2017).

## 4. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

## 5. Computational toxicology evaluation

- Cramer Classification:** Class I, Low

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

## 2. Analogs Selected:

- Genotoxicity:** Octanal dimethyl acetal (CAS # 10022-28-3)
- Repeated Dose Toxicity:** None
- Developmental and Reproductive Toxicity:** None
- Skin Sensitization:** None
- Phototoxicity/Photoallergenicity:** None
- Local Respiratory Toxicity:** None
- Environmental Toxicity:** None

- 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)

Decanal dimethyl acetal 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 that contains information on published volatile compounds which 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 10/09/2017.

## 10. Summary

### 10.1. Human health endpoint summaries

#### 10.1.1. Genotoxicity

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

#### 10.1.2. Risk assessment

Decanal dimethyl acetal was assessed in the BlueScreen assay and found to be negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no data assessing the mutagenic activity of decanal dimethyl acetal. However, read across can be made to octanal dimethyl acetal (CAS # 10022-28-3; see Section V). The mutagenic activity of octanal dimethyl acetal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA were treated with octanal dimethyl acetal in DMSO (dimethyl sulfoxide) 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, 2014a). Under the conditions of the study, octanal dimethyl acetal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of decanal dimethyl acetal. However, read across can be made to octanal dimethyl acetal (CAS # 10022-28-3; see Section V). The clastogenic activity of octanal dimethyl acetal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with octanal dimethyl acetal in DMSO (dimethyl sulfoxide) at concentrations up to 1744 µg/mL in the presence and absence of metabolic activation

(S9) at the 3-h and 24-h timepoints. Octanal dimethyl acetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014b). Under the conditions of the study, octanal dimethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, octanal dimethyl acetal does not present a concern for genotoxic potential, and this can be extended to decanal dimethyl acetal.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 10/25/2016.

#### 10.1.3. Repeated dose toxicity

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

#### 10.1.4. Risk assessment

There are no repeated dose toxicity data on decanal dimethyl acetal or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to decanal dimethyl acetal (0.23 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 03/10/2017.

#### 10.1.5. Developmental and reproductive toxicity

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

#### 10.1.6. Risk assessment

There are no developmental toxicity data on decanal dimethyl acetal or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to decanal dimethyl acetal (0.23 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laferriere et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on decanal dimethyl acetal or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to decanal dimethyl acetal (0.23 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laferriere et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 03/10/2017.

#### 10.1.7. Skin sensitization

Based on application of DST, decanal dimethyl acetal does not present a safety concern for skin sensitization under the current, declared levels of use.

#### 10.1.8. 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). No predictive skin sensitization studies are available for decanal dimethyl acetal. However, in a human maximization test, no skin sensitization reactions were observed when 4% or 2760 µg/cm<sup>2</sup> decanal dimethyl acetal in petrolatum was used for

induction and challenge (RIFM, 1977). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 µg/cm<sup>2</sup>. 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 concentration for decanal dimethyl 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:** 03/20/17.

#### 10.1.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, decanal dimethyl acetal would not be expected to present a concern for phototoxicity or photoallergenicity.

#### 10.1.10. Risk assessment

There are no phototoxicity studies available for decanal dimethyl acetal in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L · mol<sup>-1</sup> · cm<sup>-1</sup> (Henry et al., 2009). Based on lack of absorbance, decanal dimethyl acetal does not present a concern for phototoxicity or photoallergenicity.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 02/28/17.

#### 10.1.11. Local respiratory toxicity

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

#### 10.1.12. Risk assessment

There are no inhalation data available on decanal dimethyl acetal. Based on the Creme RIFM model, the inhalation exposure is 0.000086 mg/day. This exposure is 16279 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:** 3/17/2017.

### 10.2. Environmental endpoint summary

#### 10.2.1. Screening-level assessment

A screening-level risk assessment of decanal dimethyl acetal was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K<sub>ow</sub> and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use

**Table 1**  
Acceptable concentrations for decanal dimethyl acetal based on non-reactive DST–.

IFRA Category <sup>a</sup>	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% <sup>b</sup>
3	Products applied to the face using finger tips	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%
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%
8	Products with significant ano-genital exposure	0.04%	0.00%
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%	0.00%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00%

Note:

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

<sup>b</sup> Negligible exposure (< 0.01%).

Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, decanal dimethyl acetal was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify decanal dimethyl acetal as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

**10.2.1.1. Risk assessment.** Based on current Volume of Use (2011), decanal dimethyl acetal does not present a risk to the aquatic compartment in the screening-level assessment.

**10.2.1.2. Biodegradation.** No data available.

**10.2.1.3. Ecotoxicity.** No data available.

**10.2.1.4. Other available data.** Decanal dimethyl acetal has been pre-registered for REACH with no additional data at this time.

**10.2.1.5. Risk assessment refinement.** Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K <sub>ow</sub> Used	4.15	4.15
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	< 1
<b>Risk Characterization: PEC/PNEC</b>	<b>N/A</b>	<b>&lt; 1</b>

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

The RIFM PNEC is 0.004065 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: 3/8/17.**

## 11. Literature search\*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>

	LC50 (Fish)	EC50 ( <i>Daphnia</i> )	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level (Tier 1)	<u>4.065 mg/L</u>			1,000,000	<u>0.004065 µg/L</u>	



- **NTP:** [http://tools.niehs.nih.gov/ntp\\_tox/index.cfm](http://tools.niehs.nih.gov/ntp_tox/index.cfm)
  - **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://www.chem.unep.ch/irptc/sids/ocedsids/sidspub.html>
  - **EPA Actor:** <http://actor.epa.gov/actor/faces/ACToRHome.jspx;jsessionid=0EF5C212B7906229F477472A9A4D05B7>
  - **US EPA HPVIS:** <http://www.epa.gov/hpv/hpvis/index.html>
  - **US EPA Robust Summary:** <http://cfpub.epa.gov/hpv-s/>
  - **Japanese NITE:** <http://www.safe.nite.go.jp/english/db.html>
  - **Japan Existing Chemical Data Base:** [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)
  - **Google:** <https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4>
- \*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2017.10.049>.

## Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2017.10.049>.

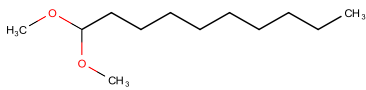
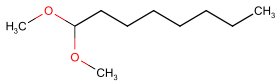
## Appendix

### 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	Decanal dimethyl acetal	Octanal dimethyl acetal
CAS No.	7779-41-1	10022-28-3
Structure		
Similarity (Tanimoto score)		0.95
Read across endpoint		• Genotoxicity
Molecular Formula	$C_{12}H_{26}O_2$	$C_{10}H_{22}O_2$
Molecular Weight	202.34	174.29
Melting Point (°C, EPISUITE)	2.05	− 20.44
Boiling Point (°C, EPISUITE)	233.71	195.26
Vapor Pressure (Pa @ 25 °C, EPISUITE)	13.4	86.4
Log Kow (KOWWIN v1.68 in EPISUITE)	4.15	3.17
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	12.12	115.3
$J_{\max}$ (mg/cm <sup>2</sup> /h, SAM)	1.290	7.570
Henry's Law (Pa·m <sup>3</sup> /mol, Bond Method, EPISUITE)	6.56E + 001	3.72E + 001
<b>Genotoxicity</b>		

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 (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
<i>In vitro</i> Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
<i>In vivo</i> mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
<b>Metabolism</b>		
OECD QSAR Toolbox (3.4)	See <a href="#">supplemental data 1</a>	See <a href="#">supplemental data 2</a>
Rat liver S9 metabolism simulator and structural alerts for metabolites		

## Summary

There are insufficient toxicity data on the target material decanal dimethyl acetal (CAS # 7779-41-1). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, octanal dimethyl acetal (CAS # 10022-28-3) was identified as a read across material with data.

## Conclusion/Rationale

- Octanal dimethyl acetal (CAS # 10022-28-3) was used as a read across analog for the target material decanal dimethyl acetal (CAS # 7779-41-1) for the genotoxicity endpoint.
  - o The target substance and the read across analog are structurally similar and belong to the structural class of saturated aliphatic acetals.
  - o The target substance and the read across analog share an alkyl dimethyl acetal substructure.
  - o The key difference between the target substance and the read across analog is that the read across analog has 2 fewer carbons in the aliphatic chain than the target. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoint.
  - o Similarity between the target substance and the read across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - o The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicity endpoints are consistent between the target substance and the read across analog.
  - o The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

## 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., Renkers, 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. Central 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, 2016. Read across assessment framework (RAAF). Retrieved from: [www.echa.europa.eu/documents/10162/13628/raaf\\_en.pdf](http://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, February 2011.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- 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), 1977. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1691 (RIFM, Woodcliff Lake, NJ, USA).
- RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of Decanal Dimethyl Acetal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 66036 (RIFM, Woodcliff Lake, NJ, USA).
- RIFM (Research Institute for Fragrance Materials, Inc), 2014a. Octanal Dimethyl Acetal: Bacterial Reverse Mutation Assay. RIFM report number 66836 (RIFM, Woodcliff Lake, NJ, USA).
- RIFM (Research Institute for Fragrance Materials, Inc), 2014b. Octanal Dimethyl Acetal: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 67295 (RIFM, Woodcliff Lake, NJ, USA).
- RIFM (Research Institute for Fragrance Materials, Inc), 2015. Use Level Survey, February 2015.
- 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., Smith, B., Thomas, R., 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.D., 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 (12), 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.