

## Short review

## RIFM fragrance ingredient safety assessment, octanal dimethyl acetal, CAS Registry Number 10022-28-3



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**Version: 100617.** This version replaces any previous versions.

**Name:** Octanal dimethyl acetal

**CAS Registry Number:** 10022-28-3

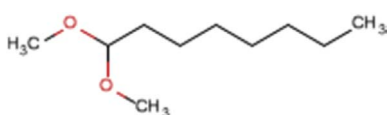
**Abbreviation/Definition list:**

**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

**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

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**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.**

Octanal dimethyl acetal was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that octanal dimethyl acetal is not genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials ( $900 \mu\text{g}/\text{cm}^2/\text{day}$ ); 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 octanal 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; octanal dimethyl acetal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, octanal dimethyl acetal was found not to be a 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 TTC.

**Reproductive Toxicity:** No

NOAEL available.  
Exposure is below 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/** (UV Spectra, RIFM DB)

**Photoallergenicity:** Not phototoxic/photoallergenic.

**Local Respiratory Toxicity:**

No NOAEC available.  
Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**

**Persistence:** Screening- (US EPA, 2012a)

Level: 3.1 (Biowin 3)

**Bioaccumulation:** (US EPA, 2012a)

Screening-Level: 57.29 L/kg

**Ecotoxicity:** Screening- (RIFM Framework; Salvito et al., 2002)

Level: Fish LC50:

22.56 mg/L

**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**

**Screening-Level:** PEC/PNEC (RIFM Framework; Salvito et al., 2002)

(North America and Europe)  $< 1$

**Critical Ecotoxicity** (RIFM Framework; Salvito et al., 2002)

**Endpoint:** Fish LC50:

22.56 mg/L

**RIFM PNEC is:** 0.02256  $\mu\text{g}/\text{L}$

• **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America

and Europe: Not applicable; cleared at screening-level

**1. Identification**

- 1. Chemical Name:** Octanal dimethyl acetal
- 2. CAS Registry Number:** 10022-28-3
- 3. Synonyms:** 1,1-Dimethoxyoctane; Aldehyde C-8 dimethyl acetal; Caprylaldehyde dimethyl acetal; Octaldehyde dimethyl acetal; Octane, 1,1-dimethoxy-; Resedyl acetal; オクタ-ルシ'メチルアセタ-ル; Octanal dimethyl acetal
- 4. Molecular Formula:**  $\text{C}_{10}\text{H}_{22}\text{O}_2$
- 5. Molecular Weight:** 174.28
- 6. RIFM Number:** 6224

**2. Physical data**

- 1. Boiling Point:** 185 °C [FMA Database], 195.26 °C [US EPA, 2012a]
- 2. Flash Point:** 168 °F; CC [FMA Database], 76 °C [GHS Database]
- 3. Log  $K_{ow}$ :** 3.17 [US EPA, 2012a]
- 4. Melting Point:** -20.44 °C [US EPA, 2012a]
- 5. Water Solubility:** 115.3 mg/L [US EPA, 2012a]
- 6. Specific Gravity:** 0.848 [FMA Database]
- 7. Vapor Pressure:** 0.45 mmHg @ 20 °C [US EPA, 2012a], 0.1 mm Hg 20C [FMA Database], 0.648 mm Hg @ 25 °C [US EPA, 2012a]

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ( $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ )
9. **Appearance/Organoleptic:** A colorless, clear liquid with a medium green, citrus, floral, leafy, rose, violet odor (Luebke, William tgsc, 1985).\*

\*<http://www.thegoodscentscompany.com/data/rw1009151.html#toorgano>, retrieved 10/21/2015.

### 3. Exposure

- Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2011)
- Maximum Level in Hydroalcoholics:** 0.037% (RIFM, 2015)
- Inhalation Exposure\*:** 0.00016 mg/kg/day or 0.011 mg/day (RIFM, 2015)
- Total Systemic Exposure\*\*:** 0.0019 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
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#### 2. Analogs Selected:

- Genotoxicity:** None
  - 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:** None

### 6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Octanal 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

Available, accessed 9/29/2017.

### 10. Summary

#### 10.1. Human health endpoint summaries

##### 10.1.1. Genotoxicity

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

**10.1.1.1. Risk assessment.** Octanal dimethyl acetal was assessed in the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). 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  $\mu\text{g}/\text{plate}$ . 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.

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  $\mu\text{g}/\text{mL}$  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.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 10/19/2016.

##### 10.1.2. Repeated dose toxicity

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

**10.1.2.1. Risk assessment.** There are no repeated dose toxicity data on octanal dimethyl acetal or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to octanal dimethyl acetal (1.9  $\mu\text{g}/\text{kg}/\text{day}$ ) is below the TTC (30  $\mu\text{g}/\text{kg bw}/\text{day}$ ; 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.

### 10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on octanal dimethyl acetal or any read across materials. The total systemic exposure to octanal 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.

**10.1.3.1. Risk assessment.** There are no developmental toxicity data on octanal dimethyl acetal or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to octanal dimethyl acetal (1.9 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler 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 octanal dimethyl acetal or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to octanal dimethyl acetal (1.9 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

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

### 10.1.4. Skin sensitization

Based on application of DST, octanal dimethyl 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). No predictive skin sensitization studies are available for octanal dimethyl acetal. Acting conservatively, due to the Insufficient 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 octanal 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.

**Table 1**

Acceptable concentrations for octanal dimethyl acetal based on non-reactive DST–.

IFRA Category <sup>a</sup>	Description of Product Type	Acceptable Concentrations in Finished Products	95 <sup>th</sup> Percentile Concentration
1	Products applied to the lips	0.069%	0.02%
2	Products applied to the axillae	0.021%	0.01%
3	Products applied to the face using finger tips	0.41%	0.00% <sup>b</sup>
4	Fine fragrance products	0.39%	0.04%
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% <sup>b</sup>
7	Products applied to the hair with some hand contact	0.79%	0.07%
8	Products with significant ano-genital exposure	0.04%	0.000%
9	Products with body and hand exposure, primarily rinse off	0.75%	0.07%
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%	0.00%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.623%

Note: <sup>a</sup>For a description of the categories, refer to the IFRA/RIFM Information Booklet.

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

### 10.1.5. Phototoxicity/photoallergenicity

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

**10.1.5.1. Risk assessment.** There are no phototoxicity studies available for octanal 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, octanal dimethyl acetal does not present a concern for phototoxicity or photoallergenicity.

**Additional References:** None.

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

### 10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, octanal dimethyl acetal, exposure level 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 octanal dimethyl acetal. Based on the Creme RIFM model, the inhalation exposure is 0.011 mg/day. This exposure is 127 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 octanal 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 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, octanal 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 octanal dimethyl acetal as either being possibly persistent nor 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).

#### 10.2.2. Risk assessment

Based on current Volume of Use (2011), octanal dimethyl 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.

Other available data:

Octanal dimethyl acetal has been pre-registered for REACH with no additional data at this time.

#### 10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 ( <i>Daphnia</i> )	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level (Tier 1)	<u>22.56 mg/L</u>			1,000,000	0.02256 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log $K_{ow}$ Used	3.17	3.17
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
<b>Risk Characterization: PEC/ PNEC</b>	<b>&lt; 1</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 0.02256 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: 3/9/17.

#### 11. Literature Search\*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECEFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>
- **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/oecdsids/sidspub.html>
- **EPA Actor:** <http://actor.epa.gov/actor/faces/ACToRHome.jsp;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.

#### Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2018.01.039>.

#### References

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