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Short review

RIFM fragrance ingredient safety assessment, Methylcyclooctyl carbonate, CAS Registry Number 61699-38-5

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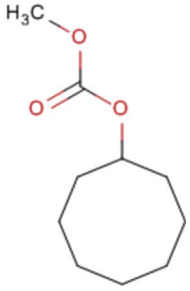
Version: 111616. This version replaces any previous versions.
Name: Isobornyl 2-methylpropionate
CAS Registry Number: 85586-67-0



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

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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
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
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.

The material (methylcyclooctyl carbonate) 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 target material (methylcyclooctyl carbonate) and the read across analog cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8) show that methylcyclooctyl carbonate is not genotoxic. Data from the read across analog cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8) show that methylcyclooctyl carbonate does not have skin sensitization potential and also provided a MOE > 100 for the repeated dose toxicity endpoint. The developmental, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on the target material (methylcyclooctyl carbonate). The environmental endpoints were evaluated, methylcyclooctyl carbonate 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, 1978a; RIFM, 1986)
Repeated Dose Toxicity: NOAEL = 167 mg/kg/day. (RIFM, 1987b)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not sensitizing. (RIFM, 1987b)
Phototoxicity/Photoallergenicity: Not phototoxic/Not photoallergenic (UV Spectra, RIFM DB; RIFM, 1976)
Local Respiratory Toxicity: No NOAEC available.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening Level: 2.78 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening Level: 92.61 l/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: 96-hr Algae EC50: 2.015 mg/l (US EPA, 2012a)
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: 96-hr Algae EC50: 2.015 mg/l (US EPA, 2012a)
RIFM PNEC is: 0.2015 µg/l
•**Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** Methylcyclooctyl carbonate
2. **CAS Registry Number:** 61699-38-5
3. **Synonyms:** Carbonic acid, cyclooctyl methyl ester; Cyclooctyl methyl carbonate; Jasmacyclat; Methylcyclooctyl carbonate
4. **Molecular Formula:** $C_{10}H_{18}O_3$
5. **Molecular Weight:** 186.25
6. **RIFM Number:** 1203

2. Physical data

1. **Boiling Point:** 47 °C [RIFM], 255.37 °C [US EPA, 2012a]
2. **Flash Point:** 119 °C [GHS], 119 °C [RIFM]
3. **Log K_{OW}:** 3.49 [US EPA, 2012a]
4. **Melting Point:** −34.49 °C [US EPA, 2012a]
5. **Water Solubility:** 54.16 mg/l [US EPA, 2012a]
6. **Specific Gravity:** 1.038 [RIFM]
7. **Vapor Pressure:** 0.0128 mmHg @ 20 °C [US EPA, 2012a], 0.0204 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 l mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a floral-herbal, very natural complex jasmine odor

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Shampoo products:** 0.0016% (RIFM, 2016)
   (No reported use in Hydroalcoholics)
3. **Inhalation Exposure*:** 0.00000010 mg/kg/day or 0.0000041 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.000021 mg/kg/day (RIFM, 2016)

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics, inhalation exposure and total exposure.

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)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	III	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1976). See Appendix below for further details.

2. **Analogs Selected:**
   a. **Genotoxicity:** Cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8)
   b. **Repeated Dose Toxicity:** Cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read across Justification:** See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Methylcyclooctyl carbonate 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, 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 7/14/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, methylcyclooctyl carbonate does not present a concern for genotoxicity.

10.1.2. Risk assessment

The mutagenic activity of methylcyclooctyl carbonate has been evaluated in a bacterial reverse mutation assay. *Salmonella typhimurium* strains TA100, TA1535, TA1537 TA1538 and TA98 were treated with methylcyclooctyl carbonate in DMSO (dimethyl sulfoxide) at concentrations up to 10,000 μg/ml. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1978a). Under the conditions of the study, methylcyclooctyl carbonate was not mutagenic in the Ames test.

There are no data assessing the clastogenicity of methylcyclooctyl carbonate. The clastogenic activity of read across material cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8; see Section 5) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage, to groups of male and female CD-1 mice. Doses up to 2850 mg/kg bodyweight were

administered. Mice from each dose level were euthanized at 24, 48, and 72 h; the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1986). Under the conditions of the study, cyclooct-4-en-1-yl methyl carbonate was considered to be not clastogenic in the *in vivo* micronucleus test and this can be extended to methylcyclooctyl carbonate.

Based on the data available, methylcyclooctyl carbonate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 1/10/2017.

10.1.3. Repeated dose toxicity

The margin of exposure for methylcyclooctyl carbonate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on methylcyclooctyl carbonate. Read across material, cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8; see Section 5) has sufficient repeated dose toxicity data. A 28-day gavage GLP study was conducted with test material, cyclooct-4-en-1-yl methyl carbonate, administered to groups of 5 CD rats/sex/dose at doses of 0 (corn oil), 20, 100 or 500 mg/kg/day. Higher relative liver weights were reported among the high dose group females. In addition, all of the treated females were reported to have an increase in relative kidney weights as compared to the control. Pallor of the kidney was reported among the mid- and high-dose group males. Microscopic changes in the kidneys of the male rats at all doses were consistent with documented changes of α-2μ globulin nephropathy, which is species-specific to the male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). The eosinophilic inclusions observed in the males receiving 500 (moderate), 100 (minimal) and 20 (minimal) mg/kg/day were not associated with evidence of degenerative changes. Similar changes were not observed in any of the treated female animals. No microscopic alterations in the liver were reported among the treated animals. Thus, the NOAEL was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 1987b).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study. The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 500/3 or 167 mg/kg/day.

Therefore, the methylcyclooctyl carbonate MOE for the repeated dose toxicity endpoint can be calculated by dividing the cyclooct-4-en-1-yl methyl carbonate NOAEL in mg/kg/day by the total systemic exposure to methylcyclooctyl carbonate, 167/0.000021 or 7952381.

Considering the molecular weight differences between the methylcyclooctyl carbonate (CAS # 61699-38-5, molecular weight = 186.25) and read across material, cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8, molecular weight = 184.35) the derived NOAEL = (186.25/184.35)*167 mg/kg/day = 169 mg/kg/day.

Therefore, the refined MOE for methylcyclooctyl carbonate can be calculated by dividing the derived NOAEL for cyclooct-4-en-1-yl methyl carbonate by the total systemic exposure to methylcyclooctyl carbonate, 169/0.000021 or 8047619.

In addition, the total systemic exposure to methylcyclooctyl carbonate (0.021 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/12/2017.

10.1.5. Developmental and reproductive toxicity

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

10.1.5.1. Risk assessment. There are no developmental and reproductive toxicity data on methylcyclooctyl carbonate or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to methylcyclooctyl carbonate a Cramer class I material (0.021 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: 01/12/2017.

10.1.6. Skin sensitization

Based on the existing data and read across cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8), methylcyclooctyl carbonate does not present a concern for skin sensitization.

10.1.6.1. Risk assessment. Limited skin sensitization studies are available for methylcyclooctyl carbonate. Based on the existing data and read across analog cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8), methylcyclooctyl carbonate does not present a concern for skin sensitization. The chemical structures of methylcyclooctyl carbonate and cyclooct-4-en-1-yl methyl carbonate indicate that they would not be predicted to be directly reactive with skin proteins (Toxtree 2.6.6; OECD toolbox v3.4). In a guinea pig maximization test methylcyclooctyl carbonate did not present reactions indicative of sensitization (RIFM, 1978b). Additionally, in a murine Local Lymph Node Assay (LLNA), read across cyclooct-4-en-1-yl methyl carbonate did not induce sensitization up to 30% (RIFM, 2004). In a human maximization test with 10% or 6900 μg/cm^2 methylcyclooctyl carbonate, no sensitization reactions were observed (RIFM, 1982a). Moreover, in a confirmatory Human Repeated Insult Patch Test (HRIPT), no reactions indicative of sensitization were observed with 2% or 1000 μg/cm^2 of read across material cyclooct-4-en-1-yl methyl carbonate (RIFM, 1985). Based on weight of evidence from structural analysis, animal and human studies, and read across cyclooct-4-en-1-yl methyl carbonate, methylcyclooctyl carbonate does not present a concern for skin sensitization.

Additional References: RIFM, 1987a; RIFM, 1982b.

Literature Search and Risk Assessment Completed on: 12/4/2015.

10.1.7. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available data, methylcyclooctyl carbonate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.7.1. Risk assessment. 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^{-1} cm^{-1} (Henry et al., 2009). In an *in vivo* phototoxicity study conducted with 3 female hairless mice, application of 5% methylcyclooctyl carbonate in olive oil did not result in phototoxic reactions following exposure to UV light (RIFM, 1976). Based on lack of significant absorbance and the available *in vivo* data, methylcyclooctyl carbonate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/28/17.

10.1.8. Local respiratory toxicity

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

10.1.8.1. Risk assessment. There are insufficient inhalation data available on methylcyclooctyl carbonate. Based on the Creme RIFM model, the inhalation exposure is 0.0000041 mg/day. This exposure is 341463 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: RIFM, 1979.

Literature Search and Risk Assessment Completed on: 12/13/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of methylcyclooctyl carbonate 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_{ow} 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 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, methylcyclooctyl carbonate was identified as a fragrance material with the 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 methylcyclooctyl carbonate 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 v4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), methylcyclooctyl carbonate presents 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. Methylcyclooctyl has been pre-registered for REACH with no additional data at this time.

11. 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 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	12.69 mg/l			1,000,000	0.01269 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.379 mg/l	5.990 mg/l	2.015 mg/l	10,000	0.2015 μg/l	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.090 mg/l	4.618 mg/l	6.065 mg/l			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.49	3.49
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.2015 μg/l. The revised PEC/PNECs for EU and NA are < 1 and, therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 12/10/15.

12. 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/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
- **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.2017.09.046.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.09.046.

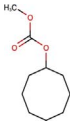
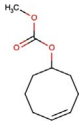
Appendix

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) and is consistent with the guidance provided by the OECD on the reporting of the defined approached used within the Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical read across assessment framework (ECHA, 2016).

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, appropriate read across analogs from the cluster were confirmed by using 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 analog were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox(v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated 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	Methylcyclooctyl carbonate	Cyclooct-4-en-1-yl methyl carbonate
CAS No.	61699-38-5	87731-18-8
Structure		

Similarity (Tanimoto score)		0.89
Read across endpoint		• Genotoxicity • Repeated dose • Skin sensitization
Molecular Formula	$C_{10}H_{18}O_3$	$C_{10}H_{16}O_3$
Molecular Weight	186.25	184.24
Melting Point (°C, EPISUITE)	−34.49	−33.45
Boiling Point (°C, EPISUITE)	47	257.63
Vapor Pressure (Pa @ 25 °C, EPISUITE)	2.72	2.41
Log Kow (KOWWIN v1.68 in EPISUITE)	3.49	3.27
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	54.16	84.57
J_{max} (mg/cm^2/h, SAM)	35.655	43.691
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.99E-003	1.75E-003
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 (low 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
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Skin Sensitization		
Protein binding by OASIS v1.4	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Sensitizer (low reliability)
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 methylcyclooctyl carbonate (CAS # 61699-38-5). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8) was identified as a read across material with data for its respective toxicity endpoints.

Conclusion/Rationale

- Cyclooct-4-en-1-yl methyl carbonate (CAS # 87731-18-8) could be used as a read across analog for the target material methylcyclooctyl carbonate (CAS # 61699-38-5) for the skin senzitization, genotoxicity and repeated dose toxicity endpoints.
  - The target substance and the read across analog are structurally similar and belong to the structural class of aliphatic carbonates.
  - The target substance and the read across analog are both eight carbon macrocyclic alcohol carbonates.
  - The key difference between the target substance and the read across analog is that the read across has an alkene group at the 4 position of the cyclooctanyl macrocycle and the target has a saturated cyclooctanyl ring. This alkene group will raise the reactivity of the read across analog slightly compared to the target substance.
  - Similarity between the target substance and the read across analog is indicated by the Tanimoto score in the table above. The Tanimoto score is mainly driven by the macrocyclic ring structure with the carbonate functional group. The differences in the structure which 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. Any differences in the physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the skin senzitization, genotoxicity and repeated dose toxicity endpoints.
  - Structural alerts for the genotoxicity and repeated dose toxicity endpoints are consistent between the target substance and the read across analog as seen in the table above. The target substance as well as the read analog are predicted to be sensitizers with low reliability only by the CAESAR model v.2.1.6. It is not predicted to react with protein by any of the other *in silico* models for skin sensitization. The data in the skin sensitization section demonstrates that the read across material is not a sensitizer, which supersedes the *in silico* prediction.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for the skin senzitization, genotoxicity and repeated dose toxicity endpoints are consistent between the metabolites of the read across analog and the target substance.

Explanation for Cramer Class

Q1. Normal constituent of the body? No

Q2. Contains functional groups associated with enhanced toxicity? N0
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) No Class Low (Class I)

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