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RIFM fragrance ingredient safety assessment, methoxycyclododecane, CAS Registry Number 2986-54-1

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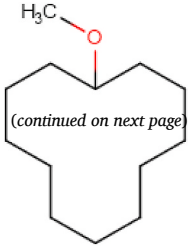

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Abbreviation/ Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

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Methoxycyclododecane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methoxycyclododecane is not genotoxic. The repeated dose and reproductive toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material; exposure is above the TTC (0.0015 mg/kg/day); therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X. Data provide methoxycyclododecane a No Expected Sensitization Induction Level (NESIL) of 1000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methoxycyclododecane is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material; exposure is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; methoxycyclododecane was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2000b; RIFM, 2017a)
Repeated Dose Toxicity: No NOAEL available. Exposure is above the TTC; therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X.
Reproductive Toxicity: No NOAEL available. Exposure is above the TTC, therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X.
Skin Sensitization: NESIL = 1000 μg/cm^2. (RIFM, 2011; Gerberick et al., 2001)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 1% (OECD 301D) RIFM (1999)
Bioaccumulation:
Screening-level: 1422 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 48-h *Daphnia magna* LC50: 0.141 mg/L (ECOSAR; US ECHA, 2012b)
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: 48-h *Daphnia magna* LC50: 0.141 mg/L (ECOSAR; US ECHA, 2012b)
RIFM PNEC is: 0.0141 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** Methoxycyclododecane
2. **CAS Registry Number:** 2986-54-1
3. **Synonyms:** Cyclododecane, methoxy-; Cyclododecyl methyl ether; Palisandin/Corps 749; Palisandin; Methoxycyclododecane
4. **Molecular Formula:** $C_{13}H_{26}O$
5. **Molecular Weight:** 198.35 g/mol
6. **RIFM Number:** 5287
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 268–270 °C at 1013 hPa (RIFM, 2014b), 261.17 °C (EPI Suite)
2. **Flash Point:** 118 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2014a), 120 °C (Globally Harmonized System)

3. **Log K_{OW}:** 5.061 ± 0.020 (25 ± 1 °C, pH 5.6) (RIFM, 2015a), 5.28 (EPI Suite)
4. **Melting Point**: 8.7 °C at 1013 hPa (RIFM, 2014b), 5.22 °C (EPI Suite)
5. **Water Solubility:** 1.373 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0158 mm Hg at 20 °C (EPI Suite v4.0), 0.0249 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.04)

1. **95**th **Percentile Concentration in Fine Fragrance*****:** 0.56% (RIFM, 2017b)
2. **Inhalation Exposure*:** 0.0027 mg/kg/day or 0.19 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.0029 mg/kg/day (RIFM, 2017b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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, 2015, 2017; Comiskey et al., 2017).

***IFRA Category 4 in Section X for maximum acceptable concentrations in finished products.

5. Derivation of systemic absorption

1. **Dermal:** 5.16% SABS

RIFM SABS testing on methoxycyclododecane [RIFM, 2021]: An *in vitro* human skin absorption study for methoxycyclododecane (CAS # 2986-54-1) was conducted following OECD TG 428 with application of 1% w/v (49.6 μg/cm^2 dose in 5 μL) in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions for 24 h. For both unoccluded and occluded conditions, 12 active-dosed diffusion cells were prepared in addition to 4 control cells (unoccluded conditions). However, data from 1 cell under occluded conditions were excluded due to repeated observations of low receptor phase levels during the study (indicating a leak from the diffusion cell). Thus, the final sample sizes were N = 12 (unoccluded) and N = 11 (occluded). At the end of 24 h, 1.58% ± 0.16% (= 0.784 ± 0.078 μg/cm^2) and 5.16% ± 0.50% (= 2.56 ± 0.25 μg/cm^2) of the applied dose permeated through the skin under unoccluded and occluded conditions, respectively. These values represent the worst-case scenario as the total methoxycyclododecane found in the epidermis, filter paper membrane support, receptor fluid, and SC tape strips 2–10. Overall recovery was 6.84% ± 0.53% and 93.0% ± 0.4% under unoccluded and occluded conditions, respectively.

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	III

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

None

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Methoxycyclododecane is not reported to occur in foods 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed on 08/13/21 (ECHA, 2017).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for methoxycyclododecane are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.000010
2	Products applied to the axillae	0.023
3	Products applied to the face/body using fingertips	0.0015
4	Products related to fine fragrances	0.43
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.018
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0046
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.000010
5D	Baby cream, oil, talc	0.0000033
6	Products with oral and lip exposure	0.000010
7		0.012

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Products applied to the hair with some hand contact	
8	Products with significant ano-genital exposure (tampon)	0.0000033
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.026
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.0092
10B	Aerosol air freshener	0.16
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0000033
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.18

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For methoxycyclododecane, the basis was the Cramer Class III threshold values for systemic toxicity.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, methoxycyclododecane does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Methoxycyclododecane was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of methoxycyclododecane 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, TA1537, and TA102 were treated with methoxycyclododecane in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000b). Under the conditions of the study, methoxycyclododecane was not mutagenic in the Ames test.

The clastogenic activity of methoxycyclododecane 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 methoxycyclododecane in ethanol at concentrations up to 1980 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 200 μg/mL in the presence and absence of metabolic activation. Methoxycyclododecane did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, methoxycyclododecane was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on methoxycyclododecane or any read-across materials. The total systemic exposure to methoxycyclododecane is above the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use. Therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X, which are based on the Cramer Class III threshold values.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on methoxycyclododecane or on any read-across materials that can be used to support the repeated dose toxicity endpoint. After refinement based on 5.16% skin absorption rate determined by an *in vitro* study (see Section V), the total systemic exposure to methoxycyclododecane (2.9 μg/kg/day) is above the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use. As such, in the absence of data, it is recommended that products containing methoxycyclododecane are limited to the maximum acceptable concentrations provided in Section X. This will ensure that the total systemic exposure to this material falls below the TTC of 1.5 μg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/08/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on methoxycyclododecane or any read-across materials. The total systemic exposure to methoxycyclododecane is above the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use. Therefore, it is recommended that products containing methoxycyclododecane are limited to the Maximum Acceptable Concentrations (MACs) provided in Section X, which are based on the Cramer Class III threshold values.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on methoxycyclododecane or on any read-across materials that can be used to support the reproductive toxicity endpoint. After refinement based on 5.16% skin absorption rate determined by an *in vitro* study (see Section V), the total systemic exposure to methoxycyclododecane (2.9 μg/kg/day) is above the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use. As such, in the absence of data, it is recommended that products containing methoxycyclododecane are limited to the maximum acceptable concentrations provided in Section X. This will ensure that the total systemic exposure to this material falls below the TTC of 1.5 μg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/08/21.

11.1.4. Skin sensitization

Based on the existing data, methoxycyclododecane is considered a skin sensitizer with a WoE NESIL of 1000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, methoxycyclododecane is considered a skin sensitizer with a NESIL of 1000 μg/cm^2. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). However, in a murine local lymph node assay (LLNA), methoxycyclododecane was found to be sensitizing with an EC3 value of 34.1% (8525 μg/cm^2) (RIFM, 2011).

These data provide WoE to classify methoxycyclododecane as a weak sensitizer. (see Table 1). However, no Confirmation of No Induction in Humans tests (CNIHs) that conform to the published protocol are currently available on methoxycyclododecane (Politano and Api, 2008). In the absence of the human data to confirm the quantitative threshold obtained from the LLNA, a default no observed effect level (NOEL) of 1000 μg/cm^2 was used in the QRA as a NESIL, as assigned by Gerberick et al. for weak sensitizers (RIFM, 2008; Gerberick et al., 2001). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020).

The EC3 value (8525 μg/cm^2) is classified as weak and assigned a conservative default NOEL of 1000 μg/cm^2 for use in the QRA (RIFM, 2008; Gerberick et al., 2001).

Additional References: RIFM, 1968.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for methoxycyclododecane in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, methoxycyclododecane does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for methoxycyclododecane is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on methoxycyclododecane. Based on the Creme RIFM Model, the inhalation exposure is 0.19 mg/day. This exposure is 2.5 times lower than the Cramer Class III TTC value of 0.47 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: 07/20/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methoxycyclododecane was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, methoxycyclododecane 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 v4.11 (US EPA, 2012a) identified methoxycyclododecane as possibly being persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria

Table 1
Data summary for methoxycyclododecane.

LLNA Weighted Mean EC3 Value (No. Studies) μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
8525 [1]	Weak	NA	NA	NA	1000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL derived from LLNA data as defined in Gerberick et al., 2001)

Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), methoxycyclododecane presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation*****: RIFM, 1999:** The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Mean biodegradation of 1% was observed after 28 days.

Ecotoxicity**: RIFM, 2000a:** The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on mean measured concentration was 0.61 mg/L. It was reported as the geometric mean of EC0/EC100.

RIFM, 2015b: The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 values based on geometric mean measured concentration for growth rate and yield were reported to be 2.47 mg/L (95% CI: 2.09–2.75 mg/L) and 1.31 mg/L (95% CI: 1.10–1.65 mg/L).

Other available data: Methoxycyclododecane has been registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

Since methoxycyclododecane has passed the screening criteria, measured data are included for completeness and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.06	5.06
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0141 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 07/26/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.58			1000000	0.00058	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	0.183	0.141	0.368	10000	0.0141	Neutral Organics

appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 02/17/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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