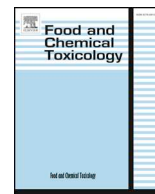




ELSEVIER

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 4-methyl-1-oxaspiro[5.5]undecene, CAS Registry Number 68228-06-8



A.M. Api^a, F. Belmonte^a, D. Belsito^b, S. Biserta^a, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, M.A. Cancellieri^a, M.L. Dagli^f, M. Date^a, W. Dekant^g, C. Deodhar^a, A.D. Fryer^h, S. Gadhia^a, L. Jones^a, K. Joshi^a, A. Lapczynski^a, M. Lavelle^a, D.C. Lieblerⁱ, M. Na^a, D. O'Brien^a, A. Patel^a, T.M. Penning^j, G. Ritacco^a, F. Rodriguez-Ropero^a, J. Romine^a, N. Sadekar^a, D. Salvito^a, T.W. Schultz^k, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m, S. Tsang^a

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

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

^c Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden

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

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

^f Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil

^g Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Wuerzburg, Germany

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

ⁱ Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

^j Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

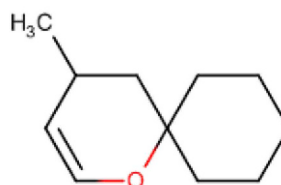
^k Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

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

^m Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

Version: 011419. This version replaces any previous versions.

Name: 4-Methyl-1-oxaspiro[5.5]undecene CAS Registry Number: 68228-06-8



* Corresponding author.

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

<https://doi.org/10.1016/j.fct.2019.111007>

Received 8 August 2019; Received in revised form 20 November 2019; Accepted 25 November 2019

Available online 27 November 2019

0278-6915/ © 2019 Elsevier Ltd. All rights reserved.

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

QRA - Quantitative Risk Assessment

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe 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.

4-Methyl-1-oxaspiro[5.5]undecene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4-methyl-1-oxaspiro[5.5]undecene is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to 4-methyl-1-oxaspiro[5.5]undecene is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the DST for non-reactive materials (900 $\mu\text{g}/\text{cm}^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4-methyl-1-oxaspiro[5.5]undecene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-methyl-1-oxaspiro[5.5]undecene 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, 2017a; RIFM, 2017b)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

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 expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment**Hazard Assessment:****Persistence:**

Screening-level: 2.6 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Screening-level: 164.2 mg/L (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: 96-h fish LC50: 0.552 mg/L (ECOSAR; US EPA, 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: 96-h fish LC50: 0.552 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0552 $\mu\text{g}/\text{L}$

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

- Chemical Name:** 4-Methyl-1-oxaspiro[5.5]undecene
- CAS Registry Number:** 68228-06-8
- Synonyms:** 1-Oxaspiro[5.5]undecene, 4-methyl-; 4-Methyl-1-oxaspiro[5.5]undec-2-ene; Oxaspiro-1-(5,5) undecane-4-methylene; Oxaspirane; 4-Methyl-1-oxaspiro[5.5]undecene
- Molecular Formula:** C₁₁H₁₈O
- Molecular Weight:** 166.26
- RIFM Number:** 5898
- Stereochemistry:** Isomer not specified. One chiral center and 2 stereoisomers possible.

2. Physical data

- Boiling Point:** 218.71 °C (EPI Suite)
- Flash Point:** 81 °C (RIFM Database), 81 °C (GHS)
- Log K_{ow}:** 3.86 (EPI Suite)
- Melting Point:** 12.06 °C (EPI Suite)
- Water Solubility:** 32.2 mg/L (EPI Suite)
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.21 mm Hg @ 25 °C (EPI Suite), 0.141 mm Hg @ 20 °C (EPI Suite v4.0)
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
- Appearance/Organoleptic:** Not Available

3. Exposure to fragrance ingredient

- Volume of Use (worldwide band):** 1–10 metric tons per day (IFRA, 2015)
- 95th Percentile Concentration in Hydroalcoholics:** 0.13% (RIFM, 2016)
- Inhalation Exposure*:** 0.00087 mg/kg/day or 0.063 mg/day (RIFM, 2016)
- Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2016)

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

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

4. Derivation of systemic absorption

- Dermal:** Assumed 80%

Name	4-Methyl-1-oxaspiro[5.5]undecene
J _{max} (mg/cm ² /h)	0.061 ¹
Skin Absorption Class	80%

¹ J_{max} was calculated based on estimated log K_{ow} = 4.29 (consensus model) and Solubility = 161 mg/L (consensus model).

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

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

5. Computational toxicology evaluation

- Cramer Classification:** Class III, High

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

- Analogs Selected:

- Genotoxicity:** None
- Repeated Dose Toxicity:** None
- 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.
Additional References:
None.

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

4-Methyl-1-oxaspiro[5.5]undecene 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None

9. REACH dossier

Pre-registered 2010; no dossier available as of 01/14/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 4-methyl-1-oxaspiro[5.5]undecene does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 4-Methyl-1-oxaspiro[5.5]undecene was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2015). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the

potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 4-methyl-1-oxaspiro[5.5]undecene 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 *Escherichia coli* strain WP2uvrA were treated with 4-methyl-1-oxaspiro[5.5]undecene in dimethyl sulfoxide (DMSO) 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, 2017a). Under the conditions of the study, 4-methyl-1-oxaspiro[5.5]undecene was not mutagenic in the Ames test.

The clastogenic activity of 4-methyl-1-oxaspiro[5.5]undecene 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 4-methyl-1-oxaspiro[5.5]undecene in DMSO at concentrations up to 1663 µg/mL in a dose range finding (DRF) study. Micronuclei analysis was conducted at concentrations up to 232 µg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. 4-Methyl-1-oxaspiro[5.5]undecene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, 4-methyl-1-oxaspiro[5.5]undecene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 4-methyl-1-oxaspiro[5.5]undecene does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/19.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4-methyl-1-oxaspiro[5.5]undecene or any read-across materials. The total systemic exposure to 4-methyl-1-oxaspiro[5.5]undecene is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4-methyl-1-oxaspiro[5.5]undecene or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 4-methyl-1-oxaspiro[5.5]undecene (1.4 µg/kg bw/day) is below the TTC (1.5 µg/kg bw/day; Kroes et al., 2007; Laferriere et al., 2012) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/19/18.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on 4-methyl-1-oxaspiro[5.5]undecene or on any read-across materials. The total systemic exposure to 4-methyl-1-oxaspiro[5.5]undecene is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-methyl-1-oxaspiro[5.5]undecene or on any read-across materials that can be used to support the reproductive toxicity endpoint. When correcting for skin absorption (see Section IV), the total systemic exposure to 4-methyl-1-oxaspiro[5.5]undecene (1.4 µg/kg bw/day) is

below the TTC (1.5 µg/kg bw/day; Kroes et al., 2007; Laferriere et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/17/18.

10.1.4. Skin sensitization

Based on the existing data and the application of the dermal sensitization threshold (DST), 4-methyl-1-oxaspiro[5.5]undecene 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 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for 4-methyl-1-oxaspiro[5.5]undecene. However, when 1550 µg/cm² of 4-methyl-1-oxaspiro[5.5]undecene in alcohol SDA39C was used for a human repeated insult patch test (HRIPT) with 35 human subjects, no skin sensitization reactions were observed (RIFM, 1975a). Likewise, when 930 µg/cm² of this material in petrolatum was used for another HRIPT with 39 human volunteers, no reactions indicative of skin sensitization were observed (RIFM, 1975b). Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm² (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). 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 maximum acceptable concentrations for 4-methyl-1-oxaspiro[5.5]undecene that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/03/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4-methyl-1-oxaspiro[5.5]undecene 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 4-methyl-1-oxaspiro[5.5]undecene in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 4-methyl-1-oxaspiro[5.5]undecene does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/19/18.

Table 1

Maximum acceptable concentrations for 4-methyl-1-oxaspiro[5.5]undecene that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category ^a	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU ^b
2	Products applied to the axillae	0.021%	0.0030%
3	Products applied to the face using fingertips	0.41%	$1.9 \times 10^{-5}\%$
4	Fine fragrance products	0.39%	0.22%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.015%
6	Products with oral and lip exposure	0.23%	NRU ^b
7	Products applied to the hair with some hand contact	0.79%	0.0050%
8	Products with significant ano-genital exposure	0.041%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.018%
10	Household care products with mostly hand contact	2.7%	0.31%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	1.6%

Note.

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.^b No reported use.^c Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 4-methyl-1-oxaspiro[5.5]undecene is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 4-methyl-1-oxaspiro[5.5]undecene. Based on the Creme RIFM Model, the inhalation exposure is 0.063 mg/day. This exposure is 7.5 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: 12/11/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4-methyl-1-oxaspiro[5.5]undecene 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, 4-methyl-1-oxaspiro[5.5]undecene 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 4-methyl-1-oxaspiro[5.5]undecene as possibly being persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥ 2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 4-methyl-1-oxaspiro[5.5]undecene 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. 4-methyl-1-oxaspiro[5.5]undecene 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 $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

Search keywords: CAS number and/or material names.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>5.402</u>			1000000	0.00540	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	<u>0.552</u>	0.913	1.139	10000	0.0552	Vinyl/Allyl Ethers

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	3.86	3.86
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is 0.0552 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: 01/03/19.

11. 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**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opphpv/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/>

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- 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.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>.
- 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), 2015. Volume of Use Survey, February 2015.
- 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.
- RIFM (Research Institute for Fragrance Materials, Inc), 1975. Repeated Insult Patch Test with 4-methyl-1-oxaspiro[5.5]undecene (Oxaspiro-1-(5,5) Undecane-4-Methylene). Unpublished Report from International Flavors and Fragrances. RIFM Report Number 54559. RIFM, Woodcliff Lake, NJ, USA.

- RIFM (Research Institute for Fragrance Materials, Inc), 1975. Repeated Insult Patch Test with 4-methyl-1-oxaspiro[5.5]undecene (Oxaspiro-1-(5,5) Undecane-4-Methylene). Unpublished Report from International Flavors and Fragrances. RIFM Report Number 54560. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2015. Report on the Testing of Palmitic Acid in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 69510. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 10, March 2016.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017. 4-Methyl-1-oxaspiro[5.5]undecene: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM Report Number 71500. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017. 4-Methyl-1-oxaspiro[5.5]undecene: in Vitro Human Lymphocyte Micronucleus Assay. RIFM Report Number 71511. RIFM, Woodcliff Lake, NJ, USA.
- Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. *Regul. Toxicol. Pharmacol.* 72 (3), 683–693.
- 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.
- 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., 2015b. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Safford, R.J., 2008. The dermal sensitisation threshold—A TTC approach for allergic contact dermatitis. *Regul. Toxicol. Pharmacol.* 51 (2), 195–200.
- Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. *Regul. Toxicol. Pharmacol.* 72 (3), 694–701.
- Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. *Regul. Toxicol. Pharmacol.* 60 (2), 218–224.
- 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.
- US EPA, 2012. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012. The ECOSAR (ECOLOGICAL Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.