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Short Review

RIFM fragrance ingredient safety assessment, 1-oxaspiro[4.5]decan-2-one, 8-methyl-, CAS Registry Number 94201-19-1

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Version: 032918. This version replaces any previous versions.

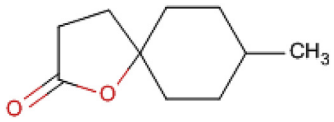
Name: 1-Oxaspiro[4.5]decan-2-one, 8-methyl-

CAS Registry Number: 94201-19-1

Additional CAS Numbers*:

91069-37-3 1-Oxaspiro[4.5]decan-2-one, 8-methyl-, cis-

*This material was included in this assessment because the materials are a mixture of isomers.



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., 2015, 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 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 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 use of this material under current conditions is supported by existing information.

1-Oxaspiro[4.5]decan-2-one, 8-methyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 1-oxaspiro[4.5]decan-2-one, 8-methyl- show that it is not genotoxic. Data from 1-oxaspiro[4.5]decan-2-one, 8-methyl- show that there are no safety concerns for skin sensitization under the current declared levels of use. Data from read-across analog 2(3H)-benzofuranone, hexahydro-3,6-dimethyl- (CAS# 92015-65-1) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to 1-oxaspiro[4.5]decan-2-one, 8-methyl- is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra and data; 1-oxaspiro[4.5]decan-2-one, 8-methyl- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-oxaspiro[4.5]decan-2-one, 8-methyl- 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, 1986; RIFM, 2015)

Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (RIFM, 1998a)

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No safety concerns for skin sensitization under the current declared levels of use. (RIFM, 1985c; RIFM, 1985d)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1985a; RIFM, 1985b)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 13% (OECD 301F) (RIFM, 2003)

Bioaccumulation: Screening-level: 16.34 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 226.9 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 226.9 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.2269 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

Chemical Name: 1-Oxaspiro [4.5]decan-2-one, 8-methyl-	**Chemical Name:** 1-Oxaspiro [4.5]decan-2-one, 8-methyl-, cis-
CAS Registry Number: 94201-19-1	**CAS Registry Number:** 91069-37-3
Synonyms: 8-Methyl-1-oxaspiro [4.5]decan-2-one; Methyl laitone; Methyl laitone (8-methyl-1-oxaspiro(4,5)decan-2-one); 1-Oxaspiro[4.5] decan-2-one, 8-methyl-	**Synonyms:** cis-1-Hydroxy-4-methylyclohexanepropanoic acid γ-lactone; cis-8-Methyl-1-oxaspiro[4.5]decan-2-one
Molecular Formula: $C_{10}H_{16}O_2$	**Molecular Formula:** $C_{10}H_{16}O_2$
Molecular Weight: 168.24	**Molecular Weight:** 168.24
RIFM Number: 7139	**RIFM Number:** 6316
Stereochemistry: Isomer not specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** Cis Isomer specified. One stereocenters and 2 total stereoisomers possible.

2. Physical data

CAS# 94201-19-1	**CAS# 91069-37-3**
Boiling Point: 278.96 °C (US EPA, 2012a)	**Boiling Point:** 278.96 °C (US EPA, 2012a)
Flash Point: > 93 °C (GHS)	**Flash Point:** Not Available
Log Kow: 2.0 (RIFM, 2013a), 2.34 (US EPA, 2012a)	**Log K_{ow}:** 2.34 (US EPA, 2012a)
Melting Point: 36.8 °C (US EPA, 2012a)	**Melting Point:** 36.8 °C (US EPA, 2012a)
Water Solubility: 624.6 mg/L (US EPA, 2012a)	**Water Solubility:** 624.6 mg/L (US EPA, 2012a)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00464 mm Hg @ 25 °C (US EPA, 2012a), 0.00258 mm Hg @ 20 °C (US EPA, 2012a)	**Vapor Pressure:** 0.00464 mm Hg @ 25 °C (US EPA, 2012a), 0.00258 mm Hg @ 20 °C (US EPA, 2012a)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)	
Appearance/Organoleptic: A colorless to pale yellow clear liquid with a lactonic, coconut, meadow, tropical, creamy, dairy, plum odor.*	**Appearance/Organoleptic:** A colorless to pale yellow clear liquid with a woody and lactonic smell.**

*http://www.thegoodscentscompany.com/data/rw1456331.html, retrieved 10/09/17.

**http://www.thegoodscentscompany.com/data/rw1548321.html, retrieved 10/09/17.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.11% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000098 mg/kg/day or 0.0069 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015, 2017; Safford et al., 2015, 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, 2017; Safford et al., 2015, 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 80%

Data from RIFM's *in silico* skin absorption model (RIFM, 2014) were used to predict the dermal penetration of 80% for 1-oxaspiro[4.5]decan-2-one, 8-methyl- as shown below.

	Chemical Name
Name	1-Oxaspiro[4.5]decan-2-one, 8-methyl-
J_{max} (mg/cm^2/h)	0.023[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on measured log K_{ow} = 2.0 (RIFM, 2013a) and calculated water solubility = 1675.61 mg/L (RIFM, 2014).

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

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

2. **Analogs Selected**:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 2(3H)-Benzofuranone, hexahydro-3,6-dimethyl- (CAS # 92015-65-1)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   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)

1-Oxaspiro[4.5]decan-2-one, 8-methyl- and 1-oxaspiro[4.5]decan-2-one, 8-methyl-, cis-are 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.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 03/22/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1-oxaspiro[4.5]decan-2-one, 8-methyl- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 1-Oxaspiro[4.5]decan-2-one, 8-methyl- was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013b). 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 on the target material. The mutagenic activity of 1-oxaspiro[4.5]decan-2-one, 8-methyl- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TA1538, and TA102 were treated with 1-oxaspiro[4.5]decan-2-one, 8-methyl- in dimethyl sulfoxide (DMSO) at concentrations up to 10360 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, 1986). Under the conditions of the study, 1-oxaspiro[4.5]decan-2-one, 8-methyl- was not mutagenic in the Ames test.

The clastogenic activity of 1-oxaspiro[4.5]decan-2-one, 8-methyl- 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 1-oxaspiro[4.5]decan-2-one, 8-methyl- in DMSO at concentrations up to 1682 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 1-Oxaspiro[4.5]decan-2-one, 8-methyl- did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the presence and absence of S9 activation (RIFM, 2015). Under the conditions of the study, 1-oxaspiro[4.5]decan-2-one, 8-methyl- was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 1-oxaspiro[4.5]decan-2-one, 8-methyl- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/29/17.

10.1.2. Repeated dose toxicity

The margin of exposure for 1-oxaspiro[4.5]decan-2-one, 8-methyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 1-oxaspiro[4.5]decan-2-one, 8-methyl-. Read-across material 2(3H)-benzofuranone, hexahydro-3,6-dimethyl- (CAS # 92015-65-1; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD 407/GLP 28-day oral gavage toxicity study was conducted in Sprague Dawley rats. Groups of

5 rats/sex/dose were administered via oral gavage daily with test material 2(3H)-benzofuranone, hexahydro-3,6-dimethyl- at doses of 0, 15, 150, or 1000 mg/kg/day in Arachis oil BP for 28 days. At 1000 mg/kg/day, there was a statistically significant increase in the relative liver weights among both males and females. High-dose females also showed a statistically significant increase in liver gamma glutamyl transpeptidase, but this was not considered to be associated with the toxicity of the test material since there were no microscopic changes or a concomitant increase in the alanine aminotransferase. Microscopic examination revealed centrilobular hepatocytes enlargement of the liver among both male and female animals dosed at 150 and 1000 mg/kg/day and in 2 males of the 15 mg/kg/day group. The liver weight increases and hepatocytes enlargement were considered to be adaptive in nature, since there was no histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage and clinical chemistry alterations (Hall et al., 2012). The increased gamma glutamyl transpeptidase activity in homogenized liver from high-dose females was also considered to be associated with this adaptive change. Patchy pallor and mottled appearance of the kidneys were observed in 1 high-dose male, and a second male at 150 mg/kg/day showed a pale kidney. Microscopic examination of high-dose males revealed an increased incidence of globular eosinophilic accumulations (hyaline droplet) in the renal proximal tubular epithelium. These kidney changes in males were consistent with documented changes of α-2μ-globulin nephropathy, which is species-specific to 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). Thus, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1998a; also available at RIFM, 1998b).

An OECD 407/GLP 28-day dietary toxicity study was conducted in Sprague Dawley rats. Groups of 5 rats/sex/dose were administered dietary admixture containing test material 2(3H)-benzofuranone, hexahydro-3,6-dimethyl- at mean achieved doses of 0, 5.5, 15.5, or 27.8 mg/kg/day for 28 days. There was a statistically significant reduction in bodyweight gain among males of the high-dose group at week 2 only. This was most likely due to a slight reduction in food consumption, and therefore, it was not considered to be adverse. There were no treatment-related adverse effects in clinical chemistry, hematological parameters, organ weight, gross pathology, and histopathology. Thus, the NOAEL for the repeated dose toxicity was considered to be 27.8 mg/kg/day, the highest dose tested (RIFM, 2000).

Since there were no treatment-related adverse effects at the highest dose levels in both the oral gavage and the dietary study, a NOAEL of 1000 mg/kg/day was selected for the repeated dose toxicity endpoint.

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 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 1000/3 or 333 mg/kg/day.

Therefore, the 1-oxaspiro[4.5]decan-2-one, 8-methyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2(3H)-benzofuranone, hexahydro-3,6-dimethyl- NOAEL in mg/kg/day by the total systemic exposure for 1-oxaspiro[4.5]decan-2-one, 8-methyl-, 333/0.0014 or 237857.

When correcting for skin absorption (see Section IV), the total systemic exposure to 1-oxaspiro[4.5]decan-2-one, 8-methyl- (1.4 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III 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: 09/26/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1-oxaspiro[4.5]decan-2-one, 8-methyl- or any read-across materials. The total systemic exposure to 1-oxaspiro[4.5]decan-2-one, 8-methyl- 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 1-oxaspiro[4.5]decan-2-one, 8-methyl- or 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 1-oxaspiro[4.5]decan-2-one, 8-methyl- (1.4 μg/kg/day) is below the TTC (1.5 μg/kg bw/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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/26/17.

10.1.4. Skin sensitization

Based on the existing data, 1-oxaspiro[4.5]decan-2-one, 8-methyl- does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, 1-oxaspiro[4.5]decan-2-one, 8-methyl- does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In guinea pigs, a maximization test did not present reactions indicative of sensitization (RIFM, 1985c). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 1000 μg/cm2 of 1-oxaspiro[4.5]decan-2-one, 8-methyl- in an unidentified vehicle, no reactions indicative of sensitization were observed in any of the 51 volunteers (RIFM, 1985d).

Based on the weight of evidence from structural analysis and animal and human studies, 1-oxaspiro[4.5]decan-2-one, 8-methyl- does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/20/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing *in vivo* data, 1-oxaspiro[4.5]decan-2-one, 8-methyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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). In guinea pig studies, 10% 1-oxaspiro[4.5]decan-2-one, 8-methyl- did not cause phototoxic or photoallergenic reactions (RIFM, 1985a; RIFM, 1985b). Based on lack of absorbance and the available *in vivo* study data, 1-oxaspiro[4.5]decan-2-one, 8-methyl- 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, $1000\,L\,mol^{-1}\cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/21/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1-oxaspiro[4.5]decan-2-one, 8-methyl- 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 1-oxaspiro[4.5]decan-2-one, 8-methyl-. Based on the Creme RIFM model, the inhalation exposure is 0.0069 mg/day. This exposure is 68.1 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: 09/30/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1-oxaspiro[4.5]decan-2-one, 8-methyl- 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, 1-Oxaspiro[4.5]decan-2-one, 8-methyl- was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.1 did not identify 1-oxaspiro[4.5]decan-2-one, 8-methyl- as possibly 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1I.

10.2.2. Risk assessment

Based on current Volume of Use (2015), 1-oxaspiro[4.5]decan-2-one, 8-methyl- does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2003: A ready biodegradability test was conducted using a manometric respirometry test according to the OECD 301F method. Under the conditions of this study, biodegradation of 13% was observed after 28 days.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 1-Oxaspiro[4.5]decan-2-one, 8-methyl- has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>226.9</u>			1,000,000	0.2269	

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

Exposure	Europe	North America
Log K_{ow} used	2.0	2.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	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 0.2269 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported

volumes of use.

Literature Search and Risk Assessment Completed On: 3/15/17.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **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://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 appropriate in the safety assessment. This is not an exhaustive list.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.06.045.

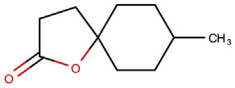
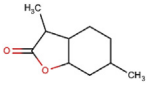
Appendix

Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material
Principal Name	1-Oxaspiro[4.5]decan-2-one, 8-methyl-	2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-
CAS No.	**94201-19-1** and 91069-37-3	92015-65-1
Structure		
Similarity (Tanimoto Score)		0.72
Read-across Endpoint		• Repeated dose
Molecular Formula	$C_{10}H_{16}O_2$	$C_{10}H_{16}O_2$
Molecular Weight	168.24	168.24
Melting Point (°C, EPI Suite)	36.80	21.70
Boiling Point (°C, EPI Suite)	278.76	276.66
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.618	152
Log Kow (KOWWIN v1.68 in EPI Suite)	2.0[1]	1.89
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	624.6	1518
J_{max} (mg/cm^2/h, SAM)	23.418	55.124
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.48E-004	2.48E-004

Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 1-oxaspiro[4.5]decan-2-one, 8-methyl- (CAS # 94201-19-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2(3H)-benzofuranone, hexahydro-3,6-dimethyl- (CAS # 92015-65-1) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 2(3H)-Benzofuranone, hexahydro-3,6-dimethyl- (CAS # 92015-65-1) was used as a read-across analog for the target material on 1-oxaspiro[4.5]decan-2-one, 8-methyl- (CAS # 94201-19-1) for the repeated dose endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of lactones.
  - ○ The target substance and the read-across analog share a common bicyclic structure.
  - ○ The key difference between the target substance and the read-across analog is that the target is a spiro bicyclic analog while the read-across is a fused bicyclic analog. This structural difference is toxicologically insignificant for the repeated dose endpoint.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the lactone moiety. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ 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 endpoint evaluated is consistent between the metabolites of the read-across analog and the target material.

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