Food and Chemical Toxicology 164 (2022) 113104

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one, CAS Registry Number 224031-70-3

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, 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*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, 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*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, 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*

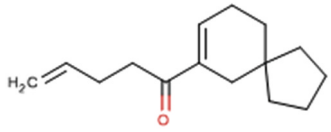
ARTICLE INFO

Handling editor: Dr. Jose Luis Domingo

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

https://doi.org/10.1016/j.fct.2022.113104
Received 4 January 2022; Received in revised form 14 April 2022; Accepted 28 April 2022
Available online 4 May 2022

Version: 122121. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one
CAS Registry Number: 224031-70-3
Additional CAS Number*:224031-71-4
4-Penten-1-one, 1-spiro[4.5]dec-6-en-7-yl-
*Included in this assessment because the materials are 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
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; Safford et al., 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 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
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

(*continued on next column*)

(*continued*)

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.

1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data showed that 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one is not genotoxic. Data on 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data provided 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one a No Expected Sensitization Induction Level (NESIL) of 50 □g/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one 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, 2012; RIFM, 2005a)
Repeated Dose Toxicity: NOAEL = 16.7 mg/kg/day. RIFM (2005b)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 50 □g/cm^2. RIFM (2006)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV/Vis Spectra, RIFM Database; RIFM, 2001a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 35% (OECD 301F; 42 days) (RIFM, 2000e)
Bioaccumulation: Critical Measured Value: BCF: 28–135 (OECD 305) RIFM (2014)
Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.11 mg/L RIFM (2007)
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: 21-day *Daphnia magna* NOEC: 0.11 mg/L RIFM (2007)
RIFM PNEC is: 2.2 □g/L
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

Chemical Name: 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one	**Chemical Name:** 4-penten-1-one, 1-spiro[4.5]dec-6-en-7-yl-
CAS Registry Number: 224031-70-3	**CAS Registry Number:** 224031-71-4
Synonyms: 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-; Spirogalbanone; 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one	**Synonyms:** Spirogalbanone
Molecular Formula: $C_{15}H_{22}O$	**Molecular Formula:** $C_{15}H_{22}O$
Molecular Weight: 218.34 g/mol	**Molecular Weight:** 218.34 g/mol
RIFM Number: 6948	**RIFM Number:** 6948

2. Physical data*

1. **Boiling Point:** Not available
2. **Flash Point:** > 93 °C (Globally Harmonized System)
3. **Log K_{OW}:** Not available
4. **Melting Point**: Not Available
5. **Water Solubility:** Not available
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.000642 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Not available

*All physical data for both materials included in this assessment are identical.

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (combined volume of both materials) (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.4)*

1. **95**th **Percentile Concentration in Fine Fragrances:** 0.011% (RIFM, 2019)
2. **Inhalation Exposure**:** 0.000026 mg/kg/day or 0.0018 mg/day (RIFM, 2019)
3. **Total Systemic Exposure***:** 0.00032 mg/kg/day (RIFM, 2019)

* 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 fine fragrance, inhalation exposure, and total exposure.

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

8. Natural occurrence

Neither 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one nor the isomer 4-penten-1-one, 1-spiro[4.5]dec-6-en-7-yl-are 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.

9. REACH dossier

HYPERLINK "https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/9939" \o "https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/9939"Available; accessed 12/21/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one 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)	0.0038
2	Products applied to the axillae	0.0011
3		0.023

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Products applied to the face/body using fingertips	
4	Products related to fine fragrances	0.021
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.0054
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0054
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.0054
5D	Baby cream, oil, talc	0.0018
6	Products with oral and lip exposure	0.013
7	Products applied to the hair with some hand contact	0.044
8	Products with significant ano-genital exposure (tampon)	0.0018
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.042
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.15
10B	Aerosol air freshener	0.15
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0018
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	72

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 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one, the basis was the subchronic reference dose of 0.167 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 50 μg/cm^2.

[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; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA were treated with 1-spiro [4.5]dec-7-en-7-yl-4-penten-1-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation (S9 mix). No significant increase in the number of revertant colonies was observed with any strain, at any dose level (RIFM, 2012). Under the conditions of the study 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one was considered not mutagenic.

The clastogenicity of 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster V79 cells were treated with 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one in ethanol at concentrations ranging up to 25 μg/mL and 62.5 μg/mL in the absence and presence, respectively, of an exogenous, metabolically active, microsomal mixture. No relevant increases in the frequencies of polyploid metaphases were found after treatment with the test material as compared to the frequencies of the controls (RIFM, 2005a). Under the experimental conditions, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one did not induce structural chromosome aberrations as determined by the chromosome aberration test in V79 cells *in vitro*.

Based on the available data, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one does not present a concern for genotoxic potential.

Additional References: RIFM, 2000f.

Literature Search and Risk Assessment Completed On: 11/23/21.

11.1.2. Repeated dose toxicity

The MOE for 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one is adequate for the repeated dose toxicity at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one. In a GLP/OECD 407-compliant study, groups of 5 Wistar rats/sex/dose were administered spirogalbanone (1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one) via gavage (vehicle: corn oil) at dose levels of 0, 50, 200, or 1000 mg/kg/day for 28 days. Additional groups of 5 rats/sex received 0 or 1000 mg/kg/day of the test material, followed by a 14-day recovery period. Clinical signs of toxicity at 1000 mg/kg/day included piloerection, sedation, hunched posture, prostration, reduced reflex, and emaciation. A statistically significant reduction in locomotor activity in high-dose animals was observed. A statistically significant decrease in mean body weight was observed in high-dose males when compared to controls. No treatment-related changes were observed in the hematology or urinalysis parameters at all dose levels. Clinical chemistry changes in high-dose animals

Table 1
Data Summary for spirogalbanone (typically a mixture of 56% of 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 40% of 4-penten-1-one, 1-spiro[4.5]dec-6-en-7-yl-). xxxxNOEL = 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 limited to 2 significant figures.

included a statistically significant increase in alanine aminotransferase and gamma-glutamyl transferase. A statistically significant increase in absolute and relative liver weight occurred at 200 and 1000 mg/kg/day. After the recovery period, the mean absolute and relative liver weights remained slightly elevated in rats treated previously with 1000 mg/kg/day; this was considered to represent a partial reversal of changes seen in these animals after the end of the treatment period. A statistically significant increase in absolute and relative kidney weight was seen in high-dose animals. Thyroid hypertrophy of the follicular epithelium in the highest-dose group was observed, with evidence suggesting slight reversibility within the 14-day recovery period. Hepatocellular hypertrophy was observed in the 200 and 1000 mg/kg/day group, which corresponded to the enlarged and discolored liver (only in the 1000 mg/kg/day treatment group) found at necropsy; this was only reversible in the high-dose group. The NOAEL for repeated dose toxicity was considered to be 50 mg/kg/day, based on a treatment-related increase in liver weights and hepatocellular hypertrophy (RIFM, 2005b).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 50/3 or 16.7 mg/kg/day.

Therefore, the 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one MOE can be calculated by dividing the 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one NOAEL in mg/kg/day by the total systemic exposure to 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one, 16.7/0.00032, or 52188.

In addition, the total systemic exposure to 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one (0.32 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1.1. Derivation of subchronic reference dose (RfD). 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) and a subchronic RfD of 0.167 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 16.7 mg/kg/day by the uncertainty factor, 100 = 0.167 mg/kg/day.

*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: 11/22/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one or any read-across materials. The total systemic exposure to 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1-spiro[4.5]dec-7-en-7-yl-4-pent-1-one (0.32 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/22/21.

11.1.4. Skin sensitization

Based on the existing data, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one is considered a moderate sensitizer with a defined NESIL of 50 μg/cm^2.

11.1.4.1. Risk assessment. Based on the material-specific data, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one isomer mixture is considered to be a moderate skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In murine local lymph node assay (LLNA), spirogalbanone (typically a mixture of 56% of 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 40% of 4-penten-1-one, 1-spiro[4.5]dec-6-en-7-yl-), non-stabilized and stabilized with 0.1% α-tocopherol was found to be sensitizing with an EC3 value of 2.24% and 2.18%, respectively (545 μg/cm^2 and 560 μg/cm^2; RIFM, 2001b; RIFM, 2001c). In a guinea pig maximization test and an open epicutaneous test, spirogalbanone did present reactions indicative of sensitization (RIFM, 2000g; RIFM, 2000h). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 0.1% or 50 μg/cm^2 spirogalbanone in 3:1 diethyl phthalate:ethanol, no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2006).

Based on WoE from structural analysis as well as animal and human studies, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one is a moderate sensitizer with a WoE NESIL of 50 μg/cm^2 (Table 1). **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) and a subchronic RfD of 0.167 mg/kg/day.**

Additional References: McKim et al., 2010; RIFM, 2000d.

Literature Search and Risk Assessment Completed On: 11/23/21.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra and *in vivo* experimental data, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra for 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one indicate no significant absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxic effects (Henry et al., 2009). Photoallergenicity of 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one was evaluated in guinea pigs, and there were no reactions indicative of photoallergenicity (RIFM, 2001a). Based on the *in vivo* experimental data and the lack of absorbance in the critical range, 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one 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 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: 11/18/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one 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 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0018 mg/day. This exposure is 261 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/18/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one 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-spiro[4.5]dec-7-en-7-yl-4-penten-1-one was identified as a fragrance material with the potential to present 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 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one as possibly 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 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), 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. **RIFM, 2000d:** The inherent biodegradability of the test material was evaluated using a manometric respirometry test according to the OECD 302C method. Under the conditions of the study, the test material underwent 17% and 21% biodegradation after 28 and 33 days, respectively.

RIFM, 2000e: A biodegradation study was conducted according to the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, the test material underwent 8% and 35% biodegradation after 28 and 42 days, respectively.

11.2.3.2. Bioaccumulation. **RIFM, 2014:** A fish bioaccumulation study was conducted with *Cyprinus carpio* following the OECD 305 guideline under flow-through conditions. The nominal concentrations of the test material in test water were 0.0075 mg/L and 0.00075 mg/L for high and low-dose, respectively. The calculated bioconcentration factors after the 28-day exposure period were 28–76 for edible parts, 61–135 for non-edible parts, and 48–104 for the whole fish.

11.2.3.3. Ecotoxicity. **RIFM, 2000a:** An acute toxicity in carp (*Cyprinus caprio*) was evaluated according to the OECD 203 method under flow-through test conditions. Under the conditions of the study, the 96-h LC50 value was reported to be 1.5 mg/L.

RIFM, 2000b: The acute toxicity of the test material to *Daphnia magna* was evaluated according to the OECD 202 method underflow-through test. Under the conditions of this study, the 48-h EC50 value was reported to be 0.26 mg/L (measured concentration).

RIFM, 2000c: An algae inhibition test was conducted using *Scenedesmus subspicatus* according to the OECD 201 guidelines. The 72-h EC50 values were reported to be 0.48 mg/L and 2.06 mg/L for biomass and rate, respectively. The 72-h NOEC value was reported to be 0.14 mg/L.

RIFM, 2007: A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under flow-through conditions. Under the conditions of the study, the 21-day NOEC value was reported to be 0.11 mg/L.

11.2.4. Other available data

1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one has been registered for REACH, with no additional data at this time.

11.2.5. 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)**	0.380			1000000	0.00038	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.657	0.156	0.177			Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.189	0.146	0.385	10000	0.0146	Neutral Organic SAR (Baseline toxicity)
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.5					
Daphnia		0.26	0.11	50	2.2	
Algae		0.48	0.14			

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	5.32	5.32
Biodegradation Factor Used	0.1	0.1
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 2.2 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 volumes of use.

Literature Search and Risk Assessment Completed On: 11/18/21.

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 appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 12/21/21.

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. November 2012 v2.1. 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.

McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-medicated gene expression in human skin cells. Cutan. Ocul. Toxicol. 29 (3), 171–192.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. 4-Penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(Spirogalbanone): 96-Hour Acute Toxicity Study in Carp (Flow-through). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60582.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. Acute Toxicity Study in Daphnia Magna with 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl- (Spirogalbanone). RIFM, Woodcliff Lake, NJ, USA [Analytical Report Attached] Unpublished report from Givaudan. RIFM report number 60584.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000c. Fresh Water Algal Growth Inhibition Test with 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl- (Spirogalbanone). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60585.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000d. Inherent Biodegradability of 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl- (Spirogalbanone). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60587.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000e. Ready Biodegradability of 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(spirogalbanone). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60588.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000f. Salmonella typhimurium Reverse Mutation Assay with 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(spirogalbanone). RIFM, Woodcliff Lake, NJ, USA [Amendment attached] Unpublished report from Givaudan. RIFM report number 60591.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000g. 4-Penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(spirogalbanone): Contact Hypersensitivity in guinea Pigs, Maximization-Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60595.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000h. 4-Penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(Spirogalbanone): Study of Skin Sensitization in the guinea Pig; Open Epicutaneous Test (Ethanol as Vehicle). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60599.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. 4-penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(spirogalbanone): Determination of Photoallergenicity in Albino guinea Pigs (Including Information about Allergenicity, Photoirritation and Irritation). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60593.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. 4-Penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(Spirogalbanone) Non-stabilized: Local Lymph Node Assay (LLNA) in Mice (Identification of Contact Allergens). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60597.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001c. 4-Penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(Spirogalbanone) Stabilized with 0.1% Alpha-Tocopherol: Local Lymph Node Assay (LLNA) in Mice (Identification of Contact Allergens). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60598.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. In Vitro Chromosome Aberration Test in Chinese Hamster V79 Cells 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(spirogalbanone). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60592.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. 4-Penten-1-one, 1-spiro [4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl-(Spirogalbanone): 28-Day Oral Toxicity (Gavage) Study in the Wistar Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60600.

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Repeated Insult Patch Test with 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5] dec-6-En-7-Yl-(spirogalbanone). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 60596.

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Daphnia Magna, Reproduction Test with 4-Penten-1-One, 1-spiro[4.5]dec-7-En-7-Yl- and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl- (Spirogalbanone). RIFM, Woodcliff Lake, NJ, USA [Analytical Report Attached] Unpublished report from Givaudan. RIFM report number 60586.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Salmonella typhimurium and Escherichia coli Reverse Mutation Assay with 1-Spiro[4.5]dec-7-En-7-Yl-4-Penten-1-One and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl- (Spirogalbanone Pure). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 64265.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014. 1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one and 4-Penten-1-One, 1-spiro[4.5]dec-6-En-7-Yl- (Spirogalbanone Pure): Bioconcentration Study in Fish. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 68294.

RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 24, March 2019.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.

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., 2015. 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.

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, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure-Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.