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Update to RIFM fragrance ingredient safety assessment, α-irone, CAS registry number 79-69-6

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*

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

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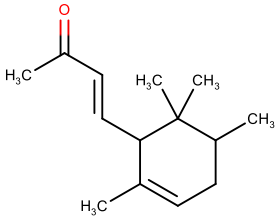
Version: 120721. This safety assessment is an updated version and replaces the previous version at https://doi.org/10.1016/j.fct.2015.03.019 **(**RIFM, 2015a**). All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.**



Name: α-Irone
CAS Registry Number: 79-69-6
Additional CAS*
54992-91-5 3-Buten-2-one, 4-[2,5,6,6-tetramethyl-1(or 2)-cyclohexen-1-yl]-
79-70-9 6-Methyl-β-ionone
*Included 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 Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

(*continued on next column*)

(*continued*)

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.

α-Irone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that α-irone is not genotoxic. Data on read-across materials β-ionone (CAS # 14901-07-6), α-ionone (CAS # 127-41-3), and (E)-β-ionone (CAS # 79-77-6) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across material (E)-β-ionone (CAS # 79-77-6) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data provided α-irone a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; α-irone is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog β-ionone (CAS # 14901-07-6). The environmental endpoints were evaluated; α-irone 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, 2000; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 10 mg/kg/day.	RIFM (1983)
Reproductive Toxicity: Developmental toxicity: NOAEL = 50 mg/kg/day. Fertility: NOAEL = 719.6 mg/kg/day.	(RIFM, 2014a; RIFM, 2004a)
Skin Sensitization: NESIL = 1700 μg/cm^2.	(RIFM, 2015b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 7.9 mg/m^3.	RIFM (2013a)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 24% (OECD 302 C) for CAS # 79-69-6	RIFM (2017b)
Bioaccumulation: Screening-level: 596.5 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia* LC50: 0.454 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: 48-h *Daphnia* LC50: 0.454 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0454 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

Chemical Name: α-Irone	**Chemical Name**: 3-Buten-2-one, 4-[2,5,6,6-tetramethyl-1	**Chemical Name**: 6-Methyl-β-ionone

(*continued on next page*)

(*continued*)

	(or 2)-cyclohexen-1-yl]-	
CAS Registry Number: 79-69-6	**CAS Registry Number:** 54992-91-5	**CAS Registry Number:** 79-70-9
Synonyms: 3-Buten-2-one, 4-(2,5,6,6-tetramethyl-2-cyclohexen-1-yl)-, *cis*-; *cis*-(2,6)-*cis*-(2(1),2(2))-α-Irone; 6-Methyl-α-ionone; 6-Methylionone; 4-(2,5,6,6-Tetramethyl-2-cyclohexen-1-yl)-3-buten-2-one; 4-(2,5,6,6-Tetramethylcyclohex-2-en-1-yl)but-3-en-2-one; Irone α; α-Irone	**Synonyms:** 4-[2,5,6,6-Tetramethyl-1(or 2)-cyclohexen-1-yl]-3-buten-2-one; Irone α; Irone F	**Synonyms:** β.-Ionone, 6-methyl-, β-Irone; 3-Buten-2-one, 4-(2,5,6,6-tetramethyl-1-cyclohexen-1-yl)-, 4-(2,5,6,6-tetramethyl-1-cyclohexen-1-yl)-3-buten-2-one; 4-(2,5,6,6-Tetramethylcyclohex-1-en-1-yl)but-3-en-2-one
Molecular Formula: $C_{14}H_{22}O$	**Molecular Formula:** $C_{14}H_{22}O$	**Molecular Formula:** $C_{14}H_{22}O$
Molecular Weight: 206.33 g/mol	**Molecular Weight:** 206.33 g/mol	**Molecular Weight:** 206.29 g/mol
RIFM Number: 336	**RIFM Number:** 6985	**RIFM Number:** 6066
Stereochemistry: *Cis* isomer specified.	**Stereochemistry:** Isomer not specified. One geometric center present, and 2 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. One geometric center present, and 2 total stereoisomers possible.

2. Physical data

CAS # 79-69-6	CAS # 54992-91-5	CAS # 79-70-9
Boiling Point: 110–112 °C (Katz, 1955), 271.32 °C (EPI Suite)	**Boiling Point:** 274.64 °C (EPI Suite)	**Boiling Point:** 274.64 °C (EPI Suite)
Flash Point: >200 °F; CC (Fragrance Materials Association [FMA] Database)	**Flash Point:** Not Available	**Flash Point:** 126 °C (Globally Harmonized System)
Log K_{OW}: 4.71 (EPI Suite), log P_{ow} = 3.8 and 4.0 (RIFM, 2010)	**Log K_{OW}:** 4.84 (EPI Suite), 3.8 and 4.0 (RIFM, 2010)	**Log K_{OW}:** 4.84 (EPI Suite)
Melting Point: 50.04 °C (EPI Suite)	**Melting Point**: 59.38 °C (EPI Suite)	**Melting Point**: 59.38 °C (EPI Suite)
Water Solubility: 3.845 mg/L (EPI Suite)	**Water Solubility:** 2.98 mg/L (EPI Suite)	**Water Solubility:** 2.98 mg/L (EPI Suite)
Specific Gravity: 0.938 (FMA Database)	**Specific Gravity:** Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00922 mm Hg at 20 °C (EPI Suite v4.0), 0.004 mm Hg 20 °C (FMA Database), 0.0147 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.00772 mm Hg at 20 °C (EPI Suite v4.0), 0.0124 mm Hg at 20 °C (FMA Database)	**Vapor Pressure:** 0.00772 mm Hg at 20 °C (EPI Suite v4.0), 0.0124 mm Hg 20 °C (FMA Database)
UV/Vis Spectra: Minor absorbance in the region 290–700 nm; molar absorption coefficients (149, 141, and 683 L $mol^{-1} \bullet cm^{-1}$, for neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$)	**UV/Vis Spectra:** Minor absorbance in the region 290–700 nm; molar absorption coefficient (570 L $mol^{-1} \bullet cm^{-1}$, condition not specified) is below the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$)	**UV/Vis Spectra:** Not available
Appearance/ Organoleptic: Arctander, 1969: Colorless or very pale straw-colored, oily liquid. The odor is soft, warm, orris-violet-like, sweet, and extremely diffusive. The taste is sweet, very powerful, and, in proper dilution, fruity/berry-like.	**Appearance/ Organoleptic:** Not Available	**Appearance/ Organoleptic:** Arctander, Volume I, 1969: Resembles β-ionone in odor, except the irone is somewhat more powerful.

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.060% (RIFM, 2019)
2. **Inhalation Exposure****: 0.00011 mg/kg/day or 0.0067 mg/day (RIFM, 2019)
3. **Total Systemic Exposure*****: 0.0011 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; Comiskey et al., 2017).

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; 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

6.1. *Cramer Classification*

Class I, Low

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

6.2. *Analogs Selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** β-ionone (CAS # 14901-07-6), α-ionone (CAS # 127-41-3), and (E)-β-ionone (CAS # 79-77-6)
c. **Reproductive Toxicity:** (E)-β-ionone (CAS # 79-77-6)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** β-ionone (CAS # 14901-07-6)
g. **Environmental Toxicity:** None

6.3. *Read-across Justification*

See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

α-Irone and its additional materials 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.

9. REACH dossier

Available for α-irone; accessed 12/07/21. No dossiers available for the additional materials as of 12/07/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for α-irone 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)	0.13
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.20
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.18
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.13
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.18
5D	Baby cream, oil, talc	0.045
6	Products with oral and lip exposure	0.067
7	Products applied to the hair with some hand contact	0.13
8	Products with significant ano-genital exposure (tampon)	0.045
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.27
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.13
10B	Aerosol air freshener	0.74
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.045
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	27

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 α-irone, the basis was the subchronic reference dose of 0.10 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1700 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).

cCalculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, α-irone does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of α-irone (CAS # 79-69-6) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with α-irone in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 using the plate incorporation method. Upon utilization of the preincubation method, an increase in revertant colony numbers was observed in TA1535 in the presence of S9. These increases were observed at the 2 highest concentrations of 2500 (4.4-fold increase) and 5000 μg/plate (10.8-fold increase). These effects were observed at cytotoxic concentrations and were considered to be biologically not relevant. No other increases in revertant colonies were observed when using the preincubation method (RIFM, 2000). Under the conditions of the study, α-irone was not mutagenic in the Ames test. As additional weight of evidence (WoE), the related material 6-methyl-β-ionone (CAS # 79-70-9) was assessed in a GLP and OECD 471 compliant Ames test using the plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 6-methyl-β-ionone 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 dose in the presence or absence of S9 (RIFM, 2012). Under the conditions of the study, 6-methyl-β-ionone was not mutagenic in the Ames test.

The clastogenic activity of additional material (isomer) 3-buten-2-one, 4-[2,5,6,6-tetramethyl-1(or 2)-cyclohexen-1-yl]- (CAS # 54992-91-5) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG487. Human peripheral blood lymphocytes were treated with 3-buten-2-one, 4-[2,5,6,6-tetramethyl-1(or 2)-cyclohexen-1-yl]- in DMSO at concentrations up to 200 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h 3-Buten-2-one, 4-[2,5,6,6-tetramethyl-1 (or 2)-cyclohexen-1-yl]- did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017a). Under the conditions of the study, 3-buten-2-one, 4-[2,5,6,6-tetramethyl-1(or 2)-cyclohexen-1-yl]- was considered to be non-clastogenic in the *in vitro* micronucleus test.

Taken together, this information indicates that α-irone does not present a concern for genotoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

The MOE for α-irone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on α-irone. Read-across materials β-ionone (CAS # 14901-07-6; see section VI), α-ionone (CAS # 127-41-3; see section VI), and (E)-β-ionone (CAS # 79-77-6; see section VI) have sufficient repeated dose toxicity data.

A 90-day dietary GLP study was conducted in Sprague Dawley rats on β-ionone (CAS # 14901-07-6). Groups of 15 rats/sex/group were fed diets containing β-ionone at concentrations of 10 or 100 mg/kg/day for

90 days, while the control group consisted of 30 rats/sex. The NOAEL was considered to be 10 mg/kg/day, based on reduced weight gain, food consumption, serum glucose concentration, increased water intake, and mild renal changes (RIFM, 1983).

In another instance, α-ionone (CAS # 127-41-3) was administered to groups of 15 Sprague Dawley rats/sex/group via diet at daily intake values of 10 or 100 mg/kg/day. The NOAEL was considered to be 10 mg/kg/day, based on reduced weight gain, food consumption, serum glucose concentration, and mild renal changes (RIFM, 1983).

(E)-β-ionone (CAS # 79-77-6) has an OECD 408/GLP dietary 90-day subchronic toxicity study conducted in rats. Groups of 10 rats/sex/dose were fed diets containing 0, 100, 1000, or 10000 ppm (equivalent to 0, 7.1, 71.8, and 719.6 mg/kg/day for males and 0, 8.2, 83.0, and 801.0 mg/kg/day for females) of test material (E)-β-ionone for 3 months. Test material-related alterations in clinical chemistry and urinalysis, along with increases in the liver and kidney weights with associated histopathological changes, were observed in the high-dose animals. Decreased thyroxine was observed in males, as well as higher degrees of severity of altered colloid in the thyroid gland of males and a high incidence with higher gradings of altered colloid in females of the high-dose group. The mid-dose animals were reported to have increased liver weights among both sexes, with associated histopathological alterations in the liver, which were considered to be adaptive and not an adverse effect. There was also an increase in urinary casts and urinary transitional epithelial cells and higher amounts of α-2u-globulin in tubular epithelial cells of the kidneys in mid-dose males. The kidney and urinary findings in males were considered to be related to α-2u-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; Lehman-McKeeman et al., 1990). The NOAEL was considered to be 1000 ppm or 71.8 and 83.0 mg/kg/day for males and females, respectively (RIFM, 2004a).

The most conservative NOAEL of 10 mg/kg/day was considered for the repeated dose toxicity endpoint.

The α-irone MOE for the repeated dose toxicity endpoint can be calculated by dividing the β-ionone NOAEL in mg/kg/day by the total systemic exposure to α-irone, 10/0.0011 or 9091.

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, 2020a) and a subchronic reference dose (RfD) of 0.10 mg/kg/day.

11.1.2.1.1. Derivation of subchronic RfD. 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 α-irone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 10 mg/kg/day by the uncertainty factor, 100 = 0.10 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/21.

11.1.3. Reproductive toxicity

The MOE for α-irone is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on α-irone. Read-across material (E)-β-ionone (CAS # 79-77-6; see section VI) has sufficient developmental toxicity data. An OECD 414/GLP-compliant gavage developmental toxicity study was conducted in Wistar rats. Groups of 25 pregnant female rats/dose were administered (E)-β-ionone daily via gavage at doses of 0, 25, 100, or 400 mg/kg/day in an olive oil vehicle on days 6–19 post-coitum. High-dose females exhibited significantly reduced food consumption on days 6–8 post-coitum, significantly reduced bodyweight gain on days 8–10 post-coitum (29% below control), and increased liver weights (29% above control). Thereafter, food uptake and weight gains of these animals reached or even exceeded control values on the days following exposure. The corrected bodyweight gain of the high-dose dams was 17% below the controls, without attaining statistical significance. The increased liver weights, which extended to mid-dose females (9% above the controls), were not considered to be adverse but as adaptive effects of metabolism. There were no effects on gestational parameters and no adverse signs of developmental toxicity up to 400 mg/kg/day, the highest dose tested. The most conservative NOAEL for maternal toxicity was considered to be 100 mg/kg/day, based on a decrease in bodyweight gain in high-dose dams. The NOAEL for developmental toxicity was considered to be 400 mg/kg/day, the highest dose tested (RIFM, 2004b).

In another study, an OECD 414/GLP dietary developmental toxicity study was conducted in New Zealand White rabbits. Groups of 22 mated female rabbits/dose were fed diets formulated to provide a target dose of 0, 50, 200, or 1000 mg/kg/day of test material (E)-β-ionone daily on days 6–29 post-coitum. Rabbits fed 1000 mg/kg/day showed severely reduced food intake after the introduction of the test diet, and as no recovery occurred up to day 10 post-coitum, these rabbits were removed from the study without further examination. An additional group of 22 mated females fed a diet at a target dose of 17 mg/kg/day were added to the study. The average compound intake was 0, 16, 50, or 160 mg/kg/day over the treatment period. At 160 mg/kg/day, reduced food consumption, reduced body weights, lower bodyweight gain, and/or bodyweight loss were observed. Fetal body weights were slightly lower at 160 mg/kg/day, which reached statistical significance for male pups only; this was considered to be secondary to the reduced food intake and markedly decreased bodyweight gain of the dams. The incidence of unossified metacarpals and/or metatarsals and unossified sternebrae were slightly higher in the fetuses at 160 mg/kg/day, which were at or just outside of the historical control values. This finding was considered to be related to the slightly lower fetal weights observed at this dose. There were no toxicologically relevant teratogenic effects on viability, litter size, sex ratio, or fetal morphological findings up the highest dose tested. The NOAEL for maternal and developmental toxicity was considered to be 50 mg/kg/day, based on reduced fetal body weight and increased incidences of 2 ossification parameters at 160 mg/kg/day (RIFM, 2014a). The most conservative NOAEL of 50 mg/kg/day was considered for the developmental toxicity endpoint. **The α-irone MOE for the developmental toxicity endpoint can be calculated by dividing the (E)-β-ionone NOAEL in mg/kg/day by the total systemic exposure to α-irone, 50/0.0011 or 45455.**

There are no fertility data on α-irone. Read-across material, (E)-β-ionone (CAS # 79-77-6; see section VI) has an OECD 408/GLP dietary 90-day subchronic toxicity study. Groups of 10 rats/sex/dose were fed diets containing 0, 100, 1000, or 10000 ppm (equivalent to 0, 7.1, 71.8, and 719.6 mg/kg/day for males and 0, 8.2, 83.0, and 801.0 mg/kg/day for females) of test material (E)-β-ionone. In addition to the systemic toxicity parameters, the thyroid hormones, estrous cycling, sperm parameters, reproductive organ weights, and histopathology (pituitary gland, adrenal glands, thyroid glands, parathyroid glands, oviducts/uterus/vagina, prostate gland, seminal vesicles, female mammary gland, testis, and epididymis) were also evaluated. There were no toxicologically significant effects observed on the reproductive parameters up to the highest dose of 10000 ppm (719.6 and 801.0 mg/kg/day for males and females, respectively). The NOAEL for fertility was considered to be 10000 ppm or 719.6 mg/kg/day, the highest dose tested (RIFM, 2004a). **Therefore, the α-irone MOE for the fertility endpoint can be calculated by dividing the (E)-β-ionone NOAEL in mg/kg/day by the total systemic exposure to α-irone, 719.6/0.0011, or 654182.**

In addition, the total systemic exposure to α-irone (1.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/08/21.

11.1.4. Skin sensitization

Based on the existing data, α-irone is considered a skin sensitizer with a defined NESIL of 1700 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, α-irone is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). α-Irone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (RIFM, 2016a; RIFM, 2016b). In a murine local lymph node assay (LLNA), β-irone was found to be sensitizing with an EC3 of 3.6% or 900 μg/cm^2 (RIFM, 2013b). In a guinea pig open epicutaneous test, no reactions indicative of sensitization were observed with α-irone (Klecak, 1979, 1985). Additionally, no reactions indicative of skin sensitization were observed in a human maximization test to α-irone (RIFM, 1972). In a Confirmation of No Induction in Humans test (CNIH) with 1772 μg/cm^2 of β-irone in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 96 volunteers (RIFM, 2015b).

Based on the WoE from structural analysis as well as animal and human studies, α-irone is a sensitizer with a WoE NESIL of 1700 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, 2020a) and a subchronic RfD of 0.10 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/28/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorbance spectra, α-irone does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for α-irone in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, α-irone 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 minor absorbance ()in the range of 290–700 nm. The molar absorption coefficients (149, 141, and 683 L mol^{-1} • cm^{-1}, for neutral, acidic, and basic conditions, respectively) are 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: 03/01/21.

Table 1
Data Summary for α-irone.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
900 [1]	Moderate	1772	NA	NA	1700

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.6. Local respiratory toxicity

There are no inhalation data available on α-irone; however, in an acute, 2-week inhalation study for read-across analog β-ionone (CAS # 14901-07-6; see section VI), a NOAEC of 7.9 mg/m^3 is reported by Randazzo (RIFM, 2013a).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week inhalation study conducted in rats, a NOAEC of 1 ppm (7.9 mg/m^3) was reported for β-ionone (RIFM, 2013a). Test substance-related microscopic findings were noted in nasal levels II, III, IV, V, and VI and included olfactory epithelial degeneration, olfactory nerve bundle degeneration (males only), inflammatory exudate or cell debris, respiratory epithelial hyperplasia, transitional epithelial hyperplasia, and subacute inflammation at the middle and highest concentrations (79 mg/m^3 and 790 mg/m^3). The NOAEC was determined to be 7.9 mg/m^3 (1 ppm), the lowest dose given.

This NOAEC expressed in mg/kg lung weight/day is:

- (7.9 mg/m^3) × (1 m^3/1000 L) = 0.0079 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0079 mg/L) × (61.2 L/day) = 0.48 mg/day
- (0.48 mg/day)/(0.0016 kg lung weight of rat*) = 300 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0067 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.01 mg/kg lung weight/day resulting in a MOE of 30000 (i.e., [300 mg/kg lung weight/day]/[0.01 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0067 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: The Union of German Candle Manufacturers, 1997; Pinching and Doving, 1974; Buchbauer et al., 1993; RIFM, 2003a; RIFM, 2003b; Rogers et al., 2003a; RIFM, 2003c; RIFM, 2003d; RIFM, 2004b; RIFM, 2004c; Isola et al., 2004a; Rogers et al., 2005; Vethanayagam et al., 2013; RIFM, 2014b.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of α-irone 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, α-irone 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 α-irone 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 v4.1). 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), α-irone presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. .

11.2.3. Biodegradation

For CAS # 79-69-6.

RIFM, 2017b: The inherent biodegradability of the test material was evaluated using the OECD 302 C guideline. Biodegradation of 11% was observed after 28 days and 24% after 62 days.

RIFM, 2011a: A manometric respirometry test according to the OECD 301F method was conducted with 30 mg/L test material. The test material undergoes 8% biodegradation after 28 days (17% after 56 days, 18% after 70 days) in the test conditions.

For CAS # 54992-91-5.

RIFM, 2011b: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 6% was observed after 28 days and 27% after 70 days.

11.2.3.2. Ecotoxicity

Not available.

11.2.3.3. Other available data

α-Irone (CAS # 79-69-6) has been registered for REACH, and no additional information is available at this time.

11.2.4. Risk assessment refinement

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.1			1000000	0.0051	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.794	0.513	0.519			Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.622	0.454	0.952	10000	0.0454	Neutral Organic SAR

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.0	4.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volumes of Use for all Cas #s.

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

The RIFM PNEC is 0.0454 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: 03/08/21.

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 12/07/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112959.

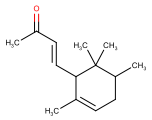
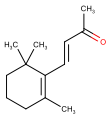
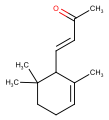
Appendix

Read-across justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020b). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (Schultz et al., 2015) and are 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, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were 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 material 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	α-Irone	β-Ionone, (E)-β-Ionone	α-Ionone
CAS No.	79-69-6	14901-07-6, 79-77-6 (isomers)	127-41-3
Structure			
Similarity (Tanimoto Score)		0.64	0.64
Endpoint		Repeated dose toxicity Reproductive toxicity (CAS 79-77-6 only) Local respiratory toxicity (CAS 14901-07-6 only)	Repeated dose toxicity
Molecular Formula	$C_{14}H_{22}O$	$C_{13}H_{20}O$	$C_{13}H_{20}O$
Molecular Weight (g/mol)	206.329	192.302	192.302
Melting Point (°C, EPI Suite)	50.04	52.45	43.06
Boiling Point (°C, EPI Suite)	271.32	262.93	259.48
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.96E+00	7.20E+00	2.31E+00
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	3.85E+00	1.69E+02	1.06E+02
Log KOW	4.71	3.84	3.84
J_{max} (μg/cm^2/h, SAM)	0.59	16.14	10.12
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.43E+01	8.20E+00	1.83E+01
Repeated dose toxicity			
Repeated Dose (HESS)	Not categorized	Vitamin A (Hepatotoxicity) Alert	Vitamin A (Hepatotoxicity) Alert
Reproductive toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2 and 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on α-irone (CAS # 79-69-6). Hence *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, (E)-β-ionone (CAS # 79-77-6), β-ionone (CAS # 14901-07-6), and α-ionone (CAS # 127-41-3) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusions

- α-Ionone (CAS # 127-41-3) was used as a read-across analog for α-irone (CAS # 79-69-6) for the repeated dose toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic ketones.
  - o The target material and the read-across analog share a methyl ionone fragment.
  - o The key difference between the target material and the read-across analog is that the target material has an additional methyl substituent on the cyclohexene ring while the read-across analog lacks it. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$40% skin absorption for the target material $\leq$80% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure to the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target material and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for reproductive toxicity endpoint are consistent between the target material and the read-across analog.
  - o The read-across analog and the target are predicted to be toxicants by the CAESAR model for developmental toxicity. The data described in the repeated dose toxicity section above show that the read-across analog has an adequate MOE at the current level of use. Therefore, the alert will be superseded by the availability of the data. The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for reproductive toxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the reproductive toxicity endpoint.
- (E)-β-Ionone (CAS # 79-77-6) and β-ionone (CAS # 14901-07-6) were used as read-across analogs for target material α-irone (CAS # 79-69-6) for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints.

- The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic ketones.
- The target material and the read-across analog share a methyl ionone fragment.
- The key difference between the target material and the read-across analog is that the read-across material has extended conjugation from the ketone group to the cyclohexene ring while the target material has does not have extended conjugation. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$40% skin absorption for the target material $\leq$80% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure to the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target material and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
- According to the QSAR OECD Toolbox (v4.2), structural alerts for the respiratory endpoint are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the respiratory endpoint are consistent between the metabolites of the read-across analog and the target material.
- The structural differences between the target material and the read-across analog do not affect consideration of the respiratory endpoint.

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