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Short review

RIFM fragrance ingredient safety assessment, methyl ionone (mixture of isomers), CAS registry number 1335-46-2

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A B S T R A C T

Methyl ionone (mixture of isomers) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from methyl ionone (mixture of isomers) show that the material is not genotoxic and provided a NESIL of 70,000 μg/cm^2 for the skin sensitization endpoint. Data provided a calculated MOE > 100 for the repeated dose toxicity and developmental toxicity endpoints, and data from read-across material (E)-β-ionone (CAS # 79-77-6) provided a calculated MOE > 100 for the reproductive toxicity endpoint. For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across material β-ionone (CAS # 14901-07-6). The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; the material is not phototoxic/photoallergenic. The environmental endpoints were evaluated with data from the target chemical and read-across material α-allylionone (CAS # 79-78-7), and the material was not found to be PBT; its risk quotients, based on current volume of use in Europe and North America (PEC/PNEC), are < 1.

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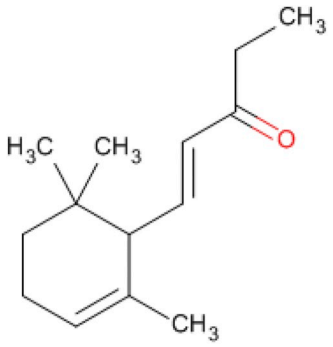
Version: 052019. This version replaces any previous versions.
Name: Methyl ionone (mixture of isomers)
CAS Registry Number: 1335-46-2



Additional CAS Numbers*:
1335-94-0 Methylionone
127-42-4 Methyl-α-ionone
79-89-0 iso-Methyl-β-ionone
127-43-5 Methyl-beta-ionone
127-51-5 α-iso-Methylionone
7779-30-8 1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one
68555-94-2 1-Penten-3-one, 2-methyl-1-(2,2,6-trimethylcyclohexenyl)-
67801-29-0 3-Methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one
15789-90-9 3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (3E)- (This CAS number has been replaced by CAS number 127-51-5)
*These materials are included in this assessment because they 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
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

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

Methyl ionone (mixture of isomers) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from methyl ionone (mixture of isomers) show that the material is not genotoxic and provided a NESIL of 70,000 μg/cm^2 for the skin sensitization endpoint. Data provided a calculated MOE > 100 for the repeated dose toxicity and developmental toxicity endpoints, and data from read-across material (E)-β-ionone (CAS # 79-77-6) provided a calculated MOE > 100 for the reproductive toxicity endpoint. For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across material β-ionone (CAS # 14901-07-6). The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; the material is not phototoxic/photoallergenic. The environmental endpoints were evaluated with data from the target chemical and read-across material α-allylionone (CAS # 79-78-7), and the material was not found to be PBT; its risk quotients, based on current volume of use in Europe and North America (PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1999a RIFM, 2000a)

Repeated Dose Toxicity: NOAEL = 30 mg/kg/day. RIFM (2006a)

Developmental and Reproductive Toxicity: Developmental toxicity NOAEL = 30 mg/kg/day. Reproductive toxicity NOAEL = 719.6 mg/kg/day. (Politano et al., 2007; RIFM, 2004a)

Skin Sensitization: NESIL = 70,000 μg/cm^2. RIFM (2004b)

Phototoxicity/Photoallergenicity: Not phototoxic/not photoallergenic.
(UV Spectra, RIFM Database; RIFM, 2017; RIFM, 1980a)

Local Respiratory Toxicity: NOAEC = 7.9 mg/m^3. RIFM (2013a)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 81% (OECD 301F) (RIFM, 2012a)

Bioaccumulation: Screening-level: 726.4 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 7-day Fish NOEC (growth): 0.35 mg/L; read-across to α-allylionone CAS # 79-78-7 RIFM (2005a)

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: 7-day Fish NOEC (growth): 0.35 mg/L: read-across to α-allylionone CAS # 79-78-7 RIFM (2005a)

RIFM PNEC is: 35 μg/L

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

1. Identification

Chemical Name	CAS Registry Number	Synonyms	Molecular Formula	Molecular Weight	RIFM Number
Methyl ionone (mixture of isomers)	1335-46-2	Ionone, methyl-; Iralia; α、β-n-ﾒﾁﾙﾖﾉﾝ; 1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en-3-one; Iraldeine; Iraldein; Raldeine A; Isoraldeine 95; Isoraldeine 70; Methylionantheme; Methylionon 70; Methyl ionone (mixture of isomers)	$C_{14}H_{22}O$	206.32	140
1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one	7779-30-8	1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en-3-one; 1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-; 5 (2,6,6-ﾄﾘﾒﾁﾙ-2-ｼｸﾛﾍｷｾﾝ-1-ｲﾙ)-4-ﾍﾟﾝﾃﾝ-3-ｵﾝ; 5 (2,6,6-トリメチル-2-シクロヘキセン-1-イル)-4-ペンテン-3-オン; α-n-ﾒﾁﾙﾖﾉﾝ	$C_{14}H_{22}O$	206.32	5363
α-iso-Methylionone	127-51-5	α-Isomethyl ionone; α-Isomethylionone; α-Methyl ionone; γ-Methylionone; 3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-; 3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one; 3-Methyl-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-en-2-one; 4-{2′,6′,6′-トリメチル-1′(又は2′)-シクロヘキセン-1′-イル}-3-アルキル(C = 1–4)-3-ブテン-2-オン; Iraldeine γ; Isoraldeine 95; Methyl Ionone α Iso; Methyl-gamma-ionone (so called); Raldeine γ	$C_{14}H_{22}O$	206.32	6273
Methyl-β-ionone	127-43-5	β-Cetone; β-Cyclocitrylidenebutanone; β-Iraldeine; β-Methylionone; 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)pent -1-en-3-one; 1-(2,6,6-Trimethylcyclohex-1-en-1-yl)pent-1-en-3-one; 1-Penten-3-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-; 5-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-4-penten-3-one; β-n-ﾒﾁﾙﾖﾉﾝ; β-n–メチルヨノン	$C_{14}H_{22}O$	206.32	6272
iso-Methyl-β-ionone	79-89-0	δ-Iraldeine; 3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-; 3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-; 3-Methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one; 3-Methyl-4-(2,6,6-trimethylcyclohex-1-enyl)but-3-en-2-one; iso-Methyl-β-ionone; Isomethyl-β-ionone; 4 - { 2′, 6′, 6′-トリメチル- 1′(又は 2′) - シクロヘキセン- 1′-イル } - 3 -アルキル (C = 1 ~ 4) - 3 -ブテン- 2 -オン	$C_{14}H_{22}O$	206.32	6083
Methyl-α-ionone	127-42-4	α-Cetone; α-Cyclocitrylidenebutanone; α-Cyclocitrylidenemethyl ethyl ketone; α-Methylionone; (R-(E))-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one; 1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en-3-one; 1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, [R-(E)]-; 5 (2,6,6-ﾄﾘﾒﾁﾙ-2-ｼｸﾛﾍｷｾﾝ-1-ｲﾙ)-4-ﾍﾟﾝﾃﾝ-3-ｵﾝ; 5 (2 , 6 , 6 -トリメチル- 2 -シクロヘキセン- 1 -イル) - 4 -ペンテン- 3 - オン; Methyl-α-ionone; α-n-ﾒﾁﾙﾖﾉﾝ; α- n - メチルヨノン	$C_{14}H_{22}O$	206.32	6250
Methylionone	1335-94-0	Irone	$C_{14}H_{22}O$	206.32	6929
1-Penten-3-one, 2-methyl-1-(2,2,-6-trimethylcyclohexenyl)-	68555-94-2	Not available	$C_{15}H_{24}O$	222.37	7334
3-Methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one	67801-29-0	3-Buten-2-one, 3-methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-; 3-Methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one; 3-Methyl-4-(2,4,6-trimethylcyclohex-3-en-1-yl) but-3-en-2-one	$C_{14}H_{22}O$	206.32	5847
3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (3E)-	15789-90-9	3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (3E)-	$C_{14}H_{22}O$	206.32	N/A

2. Physical data

1. Boiling Point:

1335-46-2	238 °C (FMA Database), 266 °C at 1013 mb (RIFM, 1990a), 274.64 °C (EPI Suite)
7779-30-8	276.02 °C (EPI Suite)
127-51-5	238 °C (FMA Database), 271.6 (EPI Suite)
127-43-5	238 °C (FMA Database), 271.6 (EPI Suite)
79-89-0	334 °C (FMA Database), 274.91 (EPI Suite)
127-42-4	238 °C (FMA Database), 276.02 (EPI Suite)
1335-94-0	276.02 °C (EPI Suite)
68555-94-2	244.00–245.00 °C. @ 760.00 mm Hg*
67801-29-0	275.46 °C (EPI Suite)
15789-90-9	N/A

2. Flash Point:

1335-46-2	126 °C (GHS), > 200 °F; CC (FMA Database)
7779-30-8	142 °C (GHS)
127-51-5	> 93 °C (GHS), > 200 °F; CC (FMA Database), 118 °C (244 °F) (BBA)
127-43-5	> 93 °C (GHS), > 200 °F
79-89-0	> 100 °C (GHS)
127-42-4	> 93 °C (GHS), > 200 °F; CC (FMA Database)
1335-94-0	Not available
68555-94-2	220.00 °F; TCC (104.44 °C)*
67801-29-0	260.00 °F; TCC (126.67 °C)*
15789-90-9	N/A

3. Log K_{OW}:

1335-46-2	Log Pow = 4.0; 4.1; 4.2 and 4.3 (RIFM, 2013b), 4.6 (at 24 °C) (RIFM, 1994a), 4.7 for n-α isomer; 4.9 for n-β isomer (RIFM, 2006b), 4.7 (RIFM, 2006c), 4.84 (EPI Suite)
7779-30-8	4.78 (EPI Suite)
127-51-5	4.84 (EPI Suite)
127-43-5	4.91 (EPI Suite)
79-89-0	4.97 (EPI Suite)
127-42-4	4.78 (EPI Suite)
1335-94-0	4.78 (EPI Suite)
68555-94-2	Log Pow = 4.918 (estimated)*
67801-29-0	4.81 (EPI Suite)
15789-90-9	N/A

4. **Melting Point**:

1335-46-2	59.38 °C (EPI Suite)
7779-30-8	53.53 °C (EPI Suite)
127-51-5	45.26 °C (EPI Suite)
127-43-5	62.86 °C (EPI Suite)
79-89-0	62 °C (EPI Suite)
127-42-4	53.53 °C (EPI Suite)
1335-94-0	53.53 °C (EPI Suite)
68555-94-2	Not available
67801-29-0	32.31 °C (EPI Suite)
15789-90-9	N/A

5. Water Solubility:

1335-46-2	almost insoluble (RIFM, 1990a), 2.98 mg/L (EPI Suite)
7779-30-8	3.328 mg/L (EPI Suite)
127-51-5	2.98 mg/L (EPI Suite)
127-43-5	2.579 mg/L (EPI Suite)
79-89-0	2.309 mg/L (EPI Suite)
127-42-4	3.328 mg/L (EPI Suite)
1335-94-0	3.328 mg/L (EPI Suite)
68555-94-2	Not available
67801-29-0	3.198 mg/L (EPI Suite)
15789-90-9	N/A

6. Specific Gravity:

1335-46-2	0.930 D20/4–0.929–0.932 (RIFM, 1990a), 0.928 (FMA Database)
7779-30-8	0.92300 to 0.93100 @ 25.00 °C*
127-51-5	0.931 (FMA Database), 0.93 g/mL (RIFM, 1994b)
127-43-5	0.933 (FMA Database)
79-89-0	Not available
127-42-4	0.93 (FMA Database)
1335-94-0	Not available
68555-94-2	0.92000 to 0.93000 @ 25.00 °C*
67801-29-0	Not available
15789-90-9	N/A

7. Vapor Pressure:

1335-46-2	0.00345 mm Hg @ 20 °C (EPI Suite v4.0), 0.005 mm Hg 20 °C (FMA Database), 0.00613 mm Hg @ 25 °C (EPI Suite)
7779-30-8	0.00367 mm Hg @ 20 °C (EPI Suite v4.0), 0.00651 mm Hg @ 20 °C (EPI Suite)
127-51-5	0.00554 mm Hg @ 20 °C (EPI Suite v4.0), 0.006 mm Hg 20 °C (FMA Database), 0.00972 mm Hg @ 25 °C (EPI Suite)
127-43-5	0.00251 mm Hg @ 20 °C (EPI Suite v4.0), 0.004 mm Hg 20 °C (FMA Database), 0.0049 mm Hg @ 25 °C (EPI Suite)
79-89-0	0.00379 mm Hg @ 20 °C (EPI Suite v4.0), 0.003 mm Hg 20 °C (FMA Database), 0.00672 mm Hg @ 25 °C (EPI Suite)
127-42-4	0.00367 mm Hg @ 20 °C (EPI Suite v4.0), 0.00651 mm Hg @ 25 °C (EPI Suite)
1335-94-0	0.00367 mm Hg @ 20 °C (EPI Suite v4.0), 0.00651 mm Hg @ 25 °C (EPI Suite)
68555-94-2	0.001000 mm Hg @ 25.00 °C (estimated)*
67801-29-0	0.00604 mm Hg@ 20 °C (EPI Suite v4.0), 0.0106 mm Hg @25 °C (EPI Suite)
15789-90-9	N/A

8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1}) for all materials.
9. **Appearance/Organoleptic:** A slightly yellow to yellow liquid with a violet-like odor.

1335-46-2	A slightly yellow to yellow liquid with a violet-like odor
7779-30-8	A pale yellow clear liquid that has a medium powdery odor described as sweet, powdery, fruity, floral, violet, beeswax, orris and woody when diluted in a 10% solution or less*
127-51-5	Almost colorless or pale straw-colored oily liquid; odor has floral notes of ylang-ylang, as well as woody notes of vetiver, and leathery notes of salicylates (Arctander, Volume II 1969)
127-43-5	Almost colorless or pale straw-colored oily liquid woody warm odor (Arctander, Volume II 1969)
79-89-0	An almost colorless or slightly yellowish oily liquid. A light and warm-woody floral with an ambregris like odor of moderate tenacity (Arctander, Volume II 1969)
127-42-4	An almost colorless or pale, straw-colored, oily liquid with a floral, sweet-oily, violet odor (Arctander, Volume II 1969)
1335-94-0	Not available
68555-94-2	A colorless to pale yellow liquid described with a medium strength described as woody, orris, violet, berry and powdery*
67801-29-0	A colorless to pale yellow clear liquid*
15789-90-9	N/A

*http://www.thegoodscentscompany.com, retrieved 06/02/2017.

3. Exposure***

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
   (combined volume of all materials)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.82% (RIFM, 2013c)
3. **Inhalation Exposure*:** 0.0011 mg/kg/day or 0.080 mg/day (RIFM, 2013c)
4. **Total Systemic Exposure**:** 0.016 mg/kg/day (RIFM, 2013c)

*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).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
   RIFM, 1984**; data also available in** Belsito et al., 2007**):** In an *in vitro* dermal penetration study, 0.7% or undetectable amounts of methyl ionone (mixture of isomers) were recovered in the receptor fluid beneath the excised skin of rats and pigs, respectively, 6 h after 600 μg/cm^2 of test material was applied over 5 cm^2 of skin. Approximately 50% (rat) and 10% (pig) of methyl ionone ^{14}C penetrated into, but not through, the epidermis and dermis, while another 30% was lost to evaporation. Thus, a dermal bioavailability of 100% was conservatively assumed for this safety assessment.
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and 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: α-Allylionone (CAS # 79-78-7)
3. Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

None of the materials included in this assessment are reported to occur in foods by the VCF*.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. REACH dossier

Methyl ionone (mixture of isomers; CAS # 1335-46-2) and α-iso-methylionone (CAS # 127-51-1) have a dossier available; accessed 06/05/17. Methyl-β-ionone (CAS # 127-43-5), 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one (CAS # 7779-30-8), α-iso-methylionone (CAS # 127-51-1), iso-methyl-β-ionone (CAS # 79-89-0), 3-methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one (CAS # 67801-29-0), and methyl-α-ionone (CAS # 127-42-4) are pre-registered for 2010.1-Penten-3-one, 2-methyl-1-(2,2,6-trimethylcyclohexenyl)- (CAS # 68555-94-2) is pre-registered for 2013. Methylionone (CAS # 1335-94-0) and 3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (3E)- (CAS # 15789-90-9) are not pre-registered. No dossier is available for these materials as of 06/06/17.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for methyl ionone (mixture of isomers) are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	5.4
2	Products applied to the axillae	1.6
3	Products applied to the face/body using fingertips	32
4	Products related to fine fragrances	30
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	7.6
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	7.6
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	7.6
5D	Baby cream, oil, talc	7.6
6	Products with oral and lip exposure	18
7	Products applied to the hair with some hand contact	61
8	Products with significant ano-genital exposure (tampon)	3.2
9	Products with body and hand exposure, primarily rinse-off (bar soap)	59
10A	Household care products with mostly hand contact (hand dishwashing detergent)	Not restricted

10B	Aerosol air freshener	Not restricted
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	Not restricted
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 methyl ionone (mixture of isomers), the basis was the reference dose of 0.30 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 70,000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, methyl ionone (mixture of isomers) does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of methyl ionone (mixture of isomers) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with methyl ionone (mixture of isomers) 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, 1999a). Under the conditions of the study, methyl ionone (mixture of isomers) was not mutagenic in the Ames test.

The clastogenic activity of methyl ionone (mixture of isomers) was evaluated using Chinese hamster ovary (CHO) cells in the presence and absence of S9 metabolic activation at doses up to 50 μg/mL. Cells were exposed for 4 and 20 h without S9 and for 4 h with an S9 activation system. No biologically significant structural chromosome aberrations were observed in the 4-h treatments in the absence or presence of S9 activation. However, statistically significant increases in structural chromosome aberrations were observed at concentrations of 12.5 and 25 μg/mL in the 20-h treatment without S9. This result was not dose responsive (RIFM, 2000a). Based on these results, methyl ionone (mixture of isomers) was concluded to be positive in the absence of S9 and negative in the presence of S9 for the induction of structural chromosome aberrations *in vitro*. These *in vitro* effects do not translate *in vivo* as demonstrated in a mouse micronucleus test where groups of male and female ICR mice were administered up to 1850 mg/kg of methyl ionone (mixture of isomers) in corn oil via intraperitoneal injection. Methyl ionone (mixture of isomers) did not induce a significant increase in micronucleated polychromatic erythrocytes in either female mice at any of the tested doses; the only statistically significant response observed was at 925 mg/kg bw in male animals. However, these increases were well within historical control range and no dose response was observed; hence, these increases were considered to be biologically not relevant (RIFM, 2000b). Furthermore, the Expert Panel for Fragrance Safety previously reviewed the ionone materials and concluded that the ionones do not possess significant *in vivo* mutagenic or genotoxic potential under the intended conditions of use as fragrance ingredients (Belsito et al., 2007).

Taken together, this information indicates that methyl ionone (mixture of isomers) does not present a concern for genetic toxicity.

Additional References: RIFM, 1980b.

Literature Search and Risk Assessment Completed On: 05/14/17.

10.1.2. Repeated dose toxicity

The margin of exposure for methyl ionone (mixture of isomers) is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl ionone (mixture of isomers). Isomer α-iso-methylionone (CAS # 127-51-5) has sufficient repeated dose toxicity data. An OECD 408/GLP gavage 90-day subchronic toxicity study was conducted on α-iso-methylionone. Groups of 10 Sprague Dawley rats/sex/dose were administered via gavage 0, 5, 30, or 500 mg/kg/day α-iso-methylionone for 90 days. Statistically significant changes in clinical chemistry parameters (reduced aspartate aminotransferase and increased plasma creatinine, total protein, and cholesterol) were observed in both sexes at 500 mg/kg/day. There were statistically significant increases in liver and kidney weights in both sexes and in spleen weights in high-dose males. Furthermore, greater incidences of thyroid (follicular cell hypertrophy in 7/10 male rats) and bone marrow (marrow hyperplasia in 10/10 male rats) histopathological changes were observed at 500 mg/kg/day. The NOAEL was considered to be 30 mg/kg/day, based on alterations in clinical chemistry parameters, organ weight, and pathological findings at the highest dose (RIFM, 2006a). **Therefore, the methyl ionone MOE for the repeated dose toxicity endpoint can be calculated by dividing the α-iso-methylionone NOAEL in mg/kg/day by the total systemic exposure to methyl ionone, 30/0.016 or 1875.**

In addition, the total systemic exposure to methyl ionone (mixture of isomers) (16 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section IX 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.30 mg/kg/day.

Derivation of reference dose (RfD):

The reference dose for methyl ionone (mixture of isomers) was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 30 mg/kg/day by the uncertainty factor, 100 = 0.30 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/17.

10.1.3. Reproductive toxicity

The margin of exposure for methyl ionone (mixture of isomers) is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on methyl ionone (mixture of isomers). Isomer α-iso-methylionone (CAS # 127-51-5) has sufficient developmental toxicity data. A developmental toxicity study was conducted in presumed pregnant rats. Groups of 25 female Sprague Dawley rats/dose were administered α-iso-

methylionone via gavage at doses of 0, 3, 10, or 30 mg/kg/day in corn oil on gestation days 7–17. There were no effects on maternal body weights, bodyweight gains, and feed consumption values. Caesarean-sectioning and litter parameters were not affected by treatment up to the highest dose tested. There were no fetal alterations observed that were considered to be associated with the test material. The NOAEL for both maternal and developmental toxicity was considered to be 30 mg/kg/day, the highest dose tested (Politano et al., 2007). **Therefore, the methyl ionone MOE for the developmental toxicity endpoint can be calculated by dividing the α-iso-methylionone NOAEL in mg/kg/day by the total systemic exposure to methyl ionone, 30/0.016 or 1875.**

There are no reproductive toxicity data on methyl ionone (mixture of isomers). An OECD 408/GLP gavage 90-day subchronic toxicity study was conducted on isomer, α-iso-methylionone (CAS # 127-51-5). Groups of 10 Sprague Dawley rats/sex/dose were administered via gavage 0, 5, 30, or 500 mg/kg/day α-iso-methylionone for 90 days. In addition to the systemic toxicity parameters, the reproductive organ weights and histopathology were also assessed. However, the function of the male and female reproductive organs was not evaluated in the study. There were no effects observed on the reproductive organs up to the highest dose of 500 mg/kg/day (RIFM, 2006a). Read-across material, (E)-β-ionone (CAS # 79-77-6; see section V) has an OECD 408/GLP dietary 90-day subchronic toxicity study conducted in Wistar 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. 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, 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 in males and females, respectively). The NOAEL for reproductive toxicity was considered to be 10000 ppm or 719.6 mg/kg/day, the highest dose tested (RIFM, 2004a). Together, these data indicate there is no concern for reproductive toxicity, and a NOAEL of 719.6 mg/kg/day was considered for the reproductive toxicity endpoint. **Therefore, the methyl ionone MOE for the reproductive toxicity endpoint can be calculated by dividing the (E)-β-ionone NOAEL in mg/kg/day by the total systemic exposure to methyl ionone, 719.6/0.016 or 44975.**

In addition, the total systemic exposure to methyl ionone (mixture of isomers) (16 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and 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: 05/25/17.

10.1.4. Skin sensitization

Based on the existing data, the methyl ionones (mixture of isomers) are considered to be weak skin sensitizers with a defined NESIL of 70,000 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, methyl ionones (mixture of isomers) are considered to be weak skin sensitizers. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4; Roberts and Natsch, 2009). α-iso-Methylionone was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA) and KeratinoSens test but positive for the human cell line activation test (h-CLAT) and U937-CD86 test (Urbisch et al., 2015; RIFM, 2015a; RIFM, 2015b; Piroird et al., 2015). In a murine local lymph node assay (LLNA), α-iso-methylionone was found to be sensitizing with an EC3 value of 21.8% (5450 μg/cm^2) (RIFM, 2005b). In guinea pigs, a Buehler test had reactions indicative of sensitization when methyl-β-ionone was diluted in ethanol (RIFM, 1989). In a confirmatory human maximization test, no skin sensitization reactions were observed (Greif, 1967). Additionally, in a confirmatory human repeated insult patch tests (HRIPT) with 70,866 μg/cm^2 of α-iso-methylionone in 1:3 diethyl phthalate:ethanol, no reactions indicative of sensitization was observed in any of the 106 volunteers (RIFM, 2004b). The available data for methyl ionones (mixture of isomers) indicates that it is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 70,000 μg/cm^2 (Table 1). Section IX 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.30 mg/kg/day.

Table 1
Data Summary for methyl ionone (mixture of isomers).

LLNA weighted mean EC3 value [No. Studies] μg/cm^2 [b]	Potency Classification Based on Animal Data [a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2 [b]	NOEL-HMT (induction) μg/cm^2 [b]	LOEL (induction) μg/cm^2 [b]	WoE NESIL [b] μg/cm^2 [b]
5450 [a]	Weak	70,866 [c]	6900	NA	70,000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

Note: [a] For a description of the categories, refer to the QRA Informational Booklet (www.rifm.org/doc/QRAInfoJuly2011.pdf).

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

[b] WoE NESIL limited to 2 significant figures.

[c] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL.

Additional References: RIFM, 1989; RIFM, 1964; RIFM, 1968; RIFM, 2005c; Klecak et al., 1977; Ishihara et al., 1986; Klecak (1985); RIFM, 2003a; RIFM, 1980a.

Literature Search and Risk Assessment Completed On: 5/23/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and *in vitro* data, methyl ionone (mixture of isomers) does not present a concern for phototoxicity. Based on UV/Vis absorbance spectra and available *in vivo* study data, methyl ionone (mixture of isomers) does not present a concern for photoallergenicity.

10.1.5.1. Risk assessment. The available UV/Vis spectra (OECD TG 101) for methyl ionone (mixture of isomers) indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is well below the benchmark (1000 L mol^{-1} · cm^{-1}) considered to be of concern for phototoxic effects (Henry et al., 2009). However, phototoxic responses were observed in exploratory studies in guinea pigs with dermal application of up to 25% methyl ionone (mixture of isomers) (RIFM,

1982a) and in Wistar rats with dermal application of 30% methyl ionone (mixture of isomers) (RIFM, 1982c; RIFM, 1982d). In an exploratory study in mice, no phototoxic responses were observed following intraperitoneal methyl ionone at 1.5 up to 660 mg/kg in olive oil (RIFM, 1982b). Information about the purity of the material tested was not available for any of these studies. Recently, a 3T3-Neutral Red Uptake (NRU) phototoxicity assay (OECD TG 432) was conducted on a sample of methyl ionone (mixture of isomers) with a documented purity > 95%, and it was not predicted phototoxic by both mean photo effect (MPE) and photo irritation factor (PIF) (RIFM, 2017). Finally, in a guinea pig photosensitization study, dermal application of 10% methyl ionone (mixture of isomers) did not result in photosensitization (RIFM, 1980a). Based on lack of absorbance in the critical UV/Vis range of the spectrum and the available *in vivo* study data, methyl ionone (mixture of isomers) does not present a concern for photoallergenicity. Based on lack of absorbance in the critical range and a 3T3-NRU phototoxicity assay on a pure sample conducted according to OECD guidelines, methyl ionone (mixture of isomers) does not present a concern for phototoxicity.

10.1.5.2. UV spectra analysis. The available UV/Vis spectra (OECD TG 101) for methyl ionone (mixture of isomers), indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark ($1000\ L\ mol^{-1} \cdot cm^{-1}$) considered to be of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/12/17.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. 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 an acute, 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^3/1000L) = 0.0079 mg/L
- Minute ventilation (MV) 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 0.080 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and 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 0.12 mg/kg lung weight/day resulting in an MOE of 2500 (i.e., [300 mg/kg lung weight/day]/[0.12 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 0.080 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, 2003b: RIFM, 2003c: Rogers et al., 2003a: RIFM, 2003d: RIFM, 2003e: RIFM, 2004c: RIFM, 2004d: Isola et al., 2004a: Rogers et al., 2005: Vethanayagam et al., 2013: RIFM, 2014.

Literature Search and Risk Assessment Completed On: 03/20/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl ionone (mixture of isomers) was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b) providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, methyl ionone (mixture of isomers) 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) did identify methyl ionone (mixture of isomers) 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). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

Based on current VoU (2015), methyl ionone (mixture of isomers) presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. For CAS # 1335-46-2.

RIFM, 2012b: A ready biodegradability study was conducted following OECD 301F guidelines. 20 mg/L of the test material was incubated for 54 days. At the end of 28 days, 81% biodegradation was observed. At the end of the study, 80% biodegradation was observed.

RIFM, 1992a: A study was conducted following OECD 302C guidelines (Modified MITI –Test II procedure). 30 mg/L of the test material was incubated for 28 days. At the end of the study, 36% biodegradation was observed.

RIFM, 1990a: A study was conducted following OECD 301C guidelines. 107 mg/L of the test substance was incubated for 28 days. At the end of 28 days, 70.5% biodegradation was observed.

RIFM, 1994c**:** A study was conducted following OECD 301B guidelines. 10 mg/L of the test substance was incubated for 28 days. At the end of 28 days, 61.8% biodegradation was observed.

RIFM, 1999b: A study was conducted following the Closed Bottle Test, Method C.4-E, according to Council Directive 92/69/EEC. 2.4 mg/L of the test substance was incubated for 28 days. At the end of 28 days, 29% biodegradation was observed.

RIFM, 2000c: A study was conducted following OECD 301F guidelines. 100 mg/L of the test substance was incubated for 28 days. At the end of 28 days, 76% biodegradation was observed.

For CAS # 127-51-5.

RIFM, 1997a: The ready biodegradability of the test material was evaluated using the Manometric Respirometry Test as per OECD 301 guidelines. The duration was 28 days, and oxygen uptake was measured. α-iso-Methylionone underwent 77% biodegradation after 28 days in the test conditions.

RIFM, 1990b: The biodegradability of α-iso-methylionone was determined by incubating the test material with activated sludge solids for 31 days according to Method F in the Blue Book Series. Fully aerobic conditions were maintained throughout the test. Biodegradation was 95.7% on day 4 and 99.1% on day 31.

RIFM, 1997b: The inherent biodegradability of the test material was determined in a sealed vessel CO_2 production test according to the OECD 302A method using an acclimatized inoculum from a modified semi-continuous activated sludge test (SCAS). The biodegradation rate after 28 days was 59.2%.

RIFM, 1993: The inherent biodegradability of α-iso-methylionone was evaluated using a sealed vessel test according to the OECD 301B method. The test duration was 56 days, and the production of CO_2 was measured. The nominal test concentration was 10 mg/L organic carbon. Biodegradation on day 56 was 63.4%.

RIFM, 1994b: The ultimate and ready biodegradability of α-iso-methyl ionone was studied using a sealed vessel test, which was conducted according to OECD 301B guidelines. α-Isomethyl ionone at 10 mg/L was incubated for 28 days, and CO_2 production was measured. The biodegradation rate at day 28 was 48.7%.

RIFM, 2012b: Biodegradation was evaluated using the Manometric Respirometry Method according to the OECD 301F guidelines. Mineral medium inoculated with activated sludge from a biological wastewater treatment plant was incubated with 30 mg/L of α-iso-methylionone for 43 days. α-iso-Methylionone underwent 71% biodegradation after 28 days.

10.2.2.1.2. Ecotoxicity. For CAS # 1335-46-2.

RIFM, 2003f: An algae growth inhibition study was conducted following OECD 201 guidelines. The 72-h EC50 was reported to be 2.89 mg/L, 3.23 mg/L and 7.47 mg/L for area under the growth, number of cells, and growth rate, respectively. The NOEC (number of cells per mL and average specific growth rate) was 1.68 mg/L, and for area under the growth curve, the NOEC was reported as 0.404 mg/L.

RIFM, 2010a: An algae growth inhibition study was conducted following OECD 201 guidelines. Under the conditions of this study, the E_rL50/E_rC50, $NOE_rLR/NOErC$, and LOE_rLR/LOE_rC were all > 9.42 mg/L (100 mg/L nominal concentration).

RIFM, 2010b: A *Daphnia* immobilization study was conducted following OECD 202 guidelines. Since the test material was poorly soluble in water, the test solutions were prepared according to the general guidance provided by the OECD to achieve a water accommodated fraction (WAF) of the test article. The 48-h EC50 was reported as 3.70 mg/L.

RIFM, 1999b: A *Daphnia magna* immobilization study was conducted using a static system and following Directive 92/69/EEC (1992) "Acute Toxicity for *Daphnia*" (C.2); the EC50 value was determined to be 5.4 mg/L at 48 h.

RIFM, 2003g: A *Daphnia magna* immobilization study was conducted following OECD 202 guidelines under static renewal conditions. The reported 48-h EC50 was 2.65 mg/L.

RIFM, 1992b: A Fish (*Onocorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 guidelines. The reported 96-h LC50 was 10.9 mg/L.

For CAS # 127-51-5.

RIFM, 1998**:** The acute toxicity of α-isomethyl ionone was evaluated in Zebra fish according to the OECD Guideline 203 guidelines under static conditions. After 96 h, the LC50 was reported to be 1.3 mg/L, based on the results of the analytically detected concentrations.

RIFM, 1995: A *Daphnia magna* immobilization test was conducted according to OECD 202 guidelines under static conditions. The EC50 value was determined to be 1.9 mg/L at 48 h.

RIFM, 1996: An acute toxicity test using a static system in *Daphnia magna* was conducted according to OECD 202 guidelines. The EC50 value was determined to be 3.7 mg/L at 48 h.

RIFM, 1997c: An algal growth inhibition test was conducted according to OECD 201 guidelines. The NOEC was considered to be 2.3 mg/L for both inhibition of rate of growth and biomass. The 72-h EC50 values were 4.4 mg/L and 5.1 mg/L for biomass and growth rate, respectively.

10.2.2.1.3. Other available data. Methyl ionone (mixture of isomers) CAS # 1335-46-2 has been registered under REACH and the following data is available:

A fish (*Brachydanio rerio*) LC50 study was conducted following OECD 203 guidelines. The 96-h LC50 for this study is 2.3 mg/L.

The following data is available for the read-across material α-allyl ionone (CAS # 79-78-7):

RIFM, 2005a: A short-term chronic static renewal toxicity test was conducted with *Daphnia magna* according to the EPA/600/4–90/002 method. The 7-day NOEC was reported to be 0.69 mg/L for both survival and reproduction.

RIFM, 2005a: A short-term chronic static renewal toxicity test was conducted with Fathead minnows. The 7-day NOEC was reported to be 0.35 mg/L for growth and 1.38 mg/L survival.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.8334			1,000,000	0.0008334	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.428	0.398	0.407			Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.476	0.351	0.774	10,000	0.0351	Neutral Organics

Tier 3: Measured Data (including Read-across)

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.3		0.35	10	35	
Daphnia		1.9	0.69			
Algae		2.89	0.404			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.9	4.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	> 1000*	> 1000*
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Regional Volume combined for all CAS #

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

The RIFM PNEC is 35 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: 03/14/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://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/

12. 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 05/22/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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.

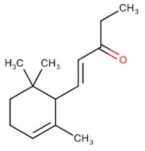
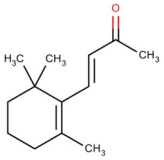
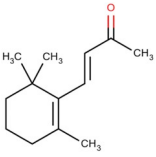
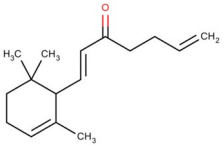
Appendix

Read-across justification

Methods

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

- Materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster were examined. Finally, appropriate read-across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints. (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analog were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target Material	Read-across material		
Principal Name	Methyl ionone (mixture of isomers)	(E)-β-Ionone	β-Ionone	Allyl α-ionone
CAS No.	**1335–46–2**, 7779-30-8, 127-51-5, 127-43-5, 79-89-0, 127-42-4, 1335-94-0, 68555-94-2, 67801-29-0	79-77-6	14901-07-6	79-78-7
Structure				
Similarity (Tanimoto score)		0.86	0.86	0.94
Read-across endpoint		•Reproductive toxicity	• Respiratory toxicity	•Environmental toxicity
Molecular Formula	$C_{14}H_{22}O$	$C_{13}H_{20}O$	$C_{13}H_{20}O$	$C_{16}H_{24}O$
Molecular Weight	206.33	192.30	192.30	232.37
Melting Point (°C, EPI Suite)	59.38	52.45	52.45	72.48
Boiling Point (°C, EPI Suite)	274.64	262.93	262.93	305.33
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.817	3.03	7.20E+000	0.364
Log Kow (KOWWIN v1.68 in EPI Suite)	4.7[1]	3.84	3.84	5.63
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2.98	169	169	0.4591
J_{max} (μg/cm^2/h, SAM)	7.043	16.143	16.143	2.069
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.87E+001	8.20E+000	8.20E+000	3.19E+001
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Toolbox (3.4)	• Non-binder without OH or NH_2 group	• Non-binder without OH or NH_2 group		
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (low reliability)	• Toxicant (low reliability)		
Respiratory				
Respiratory sensitization OECD QSAR Toolbox (3.4)	• No alert found		• No alert found	
Environmental toxicity				
BIOWIN 3	• 2.51 (possibly persistent)			• 2.45 (possibly persistent)
ECOSAR (96-h Fish LC50) for vinyl/allyl ketones in mg/L	• 1.428			• 0.402
ECOSAR (48-h *Daphnia* LC50) for vinyl/allyl ketones in mg/L	• 0.392			• 0.086
ECOSAR (96-h algae LC50) for vinyl/allyl ketones in mg/L	• 0.407			• 0.105
ECOSAR (96-h Fish LC50) for neutral organic SAR in mg/L	• 0.476			• 0.105

ECOSAR (48-h *Daphnia* LC50) for neutral organic SAR in mg/L	• 0.351				• 0.083
ECOSAR (96-h algae LC50) for neutral organic SAR in mg/L	• 0.774				• 0.248
Metabolism					
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	Supplemental Data 1		Supplemental Data 2	Supplemental Data 3	Supplemental Data 4

Summary

There are insufficient toxicity data on the methyl ionone (mixture of isomers) (CAS # 1335-46-2). Hence *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs (E)-β-ionone (CAS # 79-77-6), β-ionone (CAS # 14901-07-6), allyl α-ionone (CAS # 79-78-7), and α-iso-methylionone (CAS # 127-51-5) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- (E)-β-Ionone (CAS # 79-77-6) was used as a read-across analog for the target material methyl ionone (mixture of isomers) (CAS # 1335-46-2) for the reproductive toxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of cyclic aliphatic ketones.
  - o The target substance and the read-across analog share a cyclohexene ring with a methyl ionone fragment.
  - o The key difference between the target substance and the read-across analog is that the read-across analog has a butenone fragment while the target is pentenone fragment. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the methyl ionone fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable 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 substance, $\leq$ 80% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target substance and the 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 (v3.4), structural alerts for the reproductive toxicity endpoint are consistent between the target substance and the read-across analog.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the reproductive toxicity endpoint are consistent between the target substance 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 reproductive and developmental toxicity section above shows that the read-across analog has adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the data. The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the 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.
- β-Ionone (CAS # 14901-07-6) was used as a read-across analog for the target material methyl ionone (mixture of isomers) (CAS # 1335-46-2) for the respiratory endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of cyclic aliphatic ketones.
  - o The target substance and the read-across analog share a methyl ionone fragment.
  - o The key difference between the target substance and the read-across analog is that the read-across analog has a butenone fragment, while the target is pentenone fragment. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the methyl ionone fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable 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 substance, $\leq$ 80% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target substance 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 (v3.4), structural alerts for reproductive toxicity endpoint are consistent between the target substance and the read-across analog.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the respiratory endpoint are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o 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.

- Allyl α-ionone (CAS # 79-78-7) was used as a read-across analog for the target material methyl ionone (mixture of isomers) (CAS # 1335-46-2) for the environmental endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the structural class of cyclic aliphatic ketones.
  - The target substance and the read-across analog share a methyl ionone fragment.
  - The key difference between the target substance and the read-across analog is that the read-across analog has a butenone fragment while the target is a pentenone fragment. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the methyl ionone fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural differences between the target material and the read-across analog do not affect consideration of the environmental endpoint.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110716.

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