Food and Chemical Toxicology 97 (2016) S1–S10

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, α-Ionone, CAS Registry Number 127-41-3

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ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form
30 November 2015
Accepted 7 December 2015
Available online 17 December 2015

Keywords:
Genotoxicity
Repeated dose
Developmental and reproductive toxicity
Skin sensitization
Phototoxicity and photoallergenicity
Local respiratory toxicity
Environmental safety

ABSTRACT

The use of this material under current use conditions is supported by the existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 10 mg/kg/day. A dietary 90-day subchronic toxicity study conducted in rats resulted in a MOE of 182 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

1. Identification

1. **Chemical Name**: α-Ionone
2. **CAS Registry Number**: 127-41-3
3. **Synonyms:** 3-Buten-2-one, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, α-Cyclocitrylideneacetone, α-Ionone, α-Irisone, 4-(2,2,6-

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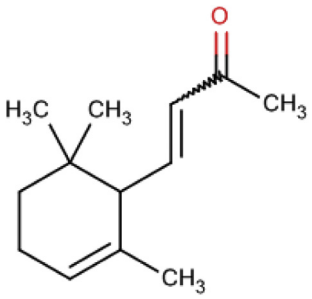
http://dx.doi.org/10.1016/j.fct.2015.12.010
0278-6915/

Version: 081715. This version replaces any previous versions.
Name: α-Ionone
CAS Registry Number: 127-41-3



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor
BCF – Bioconcentration Factor
DEREK – Derek nexus is an *in silico* tool used to identify structural alerts
DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
EU – Europe/European Union
GLP – Good Laboratory Practice
IFRA – The International Fragrance Association
LOEL – Lowest Observable Effect Level
MOE – Margin of Exposure
MPPD – Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL – No Expected Sensitization Induction Level
NOAEC – No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
NOEC – No Observed Effect Concentration
OECD – Organisation for Economic Co-operation and Development
OECD TG – Organisation for Economic Co-operation and Development Testing Guidelines
PBT – Persistent, Bioaccumulative, and Toxic
PEC/PNEC – Predicted Environmental Concentration/Predicted No Effect Concentration
QRA – quantitative risk assessment
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

Trimethyl-2-cyclohexen-1-yl)-3-buten-2-one, ヨノン, 4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one
4. **Molecular Formula**: $C_{13}H_{20}O$
5. **Molecular Weight**: 192.3
6. **RIFM Number**: 6132

2. Physical data

1. **Boiling Point:** 250 °C [FMA database], (calculated) 259.48 °C [EPI Suite]
2. **Flash Point:** >200 °F; CC [FMA database]
3. **Log K_{OW}:** 4.29 [EPI Suite]
4. **Melting Point**: (calculated) 43.06 °C [EPI Suite]
5. **Water Solubility:** 24.67 mg/L [EPI Suite]
6. **Specific Gravity**: 0.930 [FMA]
7. **Vapor Pressure:** <0.001 mm Hg 20 °C [FMA database], (calculated) 0.0173 mm Hg @ 20 °C [EPI Suite 4.0], (calculated) 0.0272 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Almost colorless or pale straw-colored to pale yellowish, oily liquid. Warm-woody, balsamic-floral odor of deep sweetness and moderate tenacity. Relatively powerful, sweet-woody taste with a fruity note. Higher concentrations, 20 ppm and up, tend to be perfumed, slightly bitter and overly woody-floral.

3. Exposure

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015; #68218) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 10 mg/kg/day. A dietary 90-day subchronic toxicity study conducted in rats resulted in a MOE of 182 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment	
Genotoxicity: Not Genotoxic	(Kasamaki et al., 1982; RIFM, 2006)
Repeated Dose Toxicity: NOAEL = 10 mg/kg/day	(RIFM, 1983)
Developmental and Reproductive Toxicity: NOAEL = 100 mg/kg/day	(RIFM, 2004a)
Skin Sensitization: Not sensitizing	(Klecak, 1985; Klecak et al., 1977; Ishihara et al., 1986)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 10 ppm or 78.65 mg/m^3 (0.079 mg/L)	(RIFM, 2013b)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 75.4% (OECD 301B)	(RIFM, 1993)
Bioaccumulation: Screening Level: 161.1 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: Read − across to (E) - β-ionone: *Daphnia* EC50: 4.03 mg/l	(RIFM, 2004b)
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; #40315)
Critical Ecotoxicity Endpoint: Read − across to (E) - β-ionone: *Daphnia* EC50: 4.03 mg/l	(RIFM, 2004b)
RIFM PNEC is: 4.03 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe <1	

1. Volume of Use (worldwide band): >1000 metric tons per year	[IFRA, 2011]
2. Average Maximum Concentration in Hydroalcoholics: 1.0%	[IFRA, 2002]
3. 97.5th **Percentile:** 2.01%	[IFRA, 2002]
4. Dermal Exposure*: 0.0512 mg/kg/day	[IFRA, 2002]
5. Oral Exposure: Not available	
6. Inhalation Exposures:** 0.004 mg/kg/day	[IFRA, 2002]
7. Total Systemic Exposure (Dermal + Inhalation): 0.055 mg/kg/day	

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available − not considered.
3. **Inhalation**: Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.055 mg/kg/day

5. Computational toxicology evaluation

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

Expert judgment	Toxtree v.2.6	OECD QSAR toolbox v.3.1
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:** Ionone (mixed isomers) (CAS # 8013-90-9)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: β-Ionone (CAS # 14901-07-6)
   g. **Environmental Toxicity:** Ionones fragrance structural group
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)

α-Ionone is reported to occur in the following foods* and in some natural complex substances (NCS):

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 8/17/2015.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, α-Ionone does not present a concern for genetic toxicity.

10.1.2. Risk assessment

The genotoxic potential of α-Ionone has been evaluated by the BlueScreen assay and was found to be not genotoxic, both with and without metabolic activation. This material was found to be not mutagenic in an Ames study; however, it was tested at low doses and only two strains of *S. typhimurium* were used (Kasamaki et al., 1982). Further evidence that α-Ionone is not mutagenic can be provided by the Ionones SAR Category. RIFM's Expert Panel concluded that overall, the ionones do not have a mutagenic potential in bacteria *in vitro* studies (Belsito et al., 2007). For the ionones, all Ames standard assays using *S. typhimurium* with and without metabolic activation were negative. Only in a non-standard Ames test, in which the TA1535 strain contained a plasmid carrying the fused gene umuC'- lac2, was one of the ionones (β-ionone) reported to have mutagenic activity (Ono et al., 1991). The Panel indicated that the utility of this assay for predicting mutagenic potential is questionable given that a number of chemicals considered to be non-mutagenic were also reportedly positive in this assay.

For α-ionone, there is a structural alert for chromosome damage, according to DEREK. A mouse micronucleus test, conducted according to OECD TG 474, was performed with α-ionone in order to evaluate the biological significance of a positive *in vitro* chromosome aberration assay (Kasamaki et al., 1982). α-Ionone was administered at doses up to 1200 mg/kg in corn oil by intraperitoneal injection to male and female ICR mice. Reductions in the ratio of polychromatic erythrocytes to total erythrocytes, relative to the respective vehicle controls suggest the bioavailability of α -ionone to the bone marrow. There were no statistically significant increases in the incidence of micronucleated polychromatic erythrocytes in α-ionone treated groups relative to their respective vehicle control in either male or female mice, regardless of dose level or bone marrow collection time. α-Ionone was concluded to be negative in the mouse micronucleus test, and therefore is considered to be not clastogenic (RIFM, 2006). Taken together, these data indicate that α-Ionone does not have the potential to be genotoxic.

Additional References: McGinty et al., 2007.

Literature Search and Risk Assessment Completed on: 05/03/13.

10.1.3. Repeated dose toxicity

The margin of exposure for α-ionone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

The repeated dose toxicity data on α-ionone are sufficient for the repeated dose toxicity endpoint. In a dietary 90-day subchronic toxicity study conducted in rats, the NOAEL was determined to be 10 mg/kg/day, based on reduced weight gain, food consumption and serum glucose concentration, increased water intake, and mild renal changes (RIFM, 1983). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 10/0.055 or 182.

Additional References: Lalko et al., 2007a; Belsito et al., 2007; Oser et al., 1965; Bar and Griepentrog, 1967; Verrett et al., 1980; Prelog et al., 1951; Longenecker et al., 1939; Hartman et al., 1988; Lalko et al., 2007b; Liu et al., 2010; Vieira et al., 2011; RIFM, 2013a; Kirkpatrick et al., 2014; Willhite, 1986; Gomes-Carneiro et al., 2003; Fell et al., 1962; Ide and Toki, 1970; Bielig and Hayasida, 1940; Prelog and Meier, 1950; Lalko et al., 2007c; RIFM, 2003a; RIFM, 2004; Lalko et al., 2007d; Shillinger, 1950; Sporn et al., 1963; Sporn, 1964; Hagan et al., 1967.

Literature Search and Risk Assessment Completed on: 05/03/13.

Acerola (Malpighia)	Cardamom (Ellettaria cardamomum Maton.)
Almond (roasted) (Prunus amygdalus)	Carrot (Daucus carota L.)
Apricot (Prunus armeniaca L.)	Celery (Apium graveolens L.)
Beans	Chinese quince (Pseudocydonia sinensis Schneid)
Buckwheat	Cider (apple wine)
Citrus fruits	Raspberry, blackberry and boysenberry
Grape brandy	Strawberry (Fragaria species)
Kumazasa (Sasa albo-marginata)	Tamarind (Tamarindus indica L.)
Loganberry (Rubus ursinus var. loganobaccus)	Tapereba, caja fruit (Spondias lutea L.)
Macadamia nut (Macadamia integrifolia)	Tea
Mate (Ilex paraguayensis)	Thyme (Thymus species)
Melon	Tomato (Lycopersicon esculentum Mill.)
Passion fruit (Passiflora species)	Whisky
Peas (Pisum sativum L.)	Wine
Raspberry brandy	

*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for α-ionone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on α-ionone. Isomer (E)-β-ionone (CAS # 79-77-6; see Section 5) has an OECD 414 gavage developmental toxicity study in rats, which showed no teratogenic effects and concluded a NOAEL of 400 mg/kg/day for developmental toxicity, the highest dosage tested (RIFM, 2004a). Therefore, the MOE for developmental toxicity is equal to the (E)-β-ionone NOAEL in mg/kg/day divided by the total systemic exposure, 400/0.055 or 7273.

There are no reproductive toxicity data on α-ionone. The OECD 414 gavage developmental toxicity study on isomer (E)-β-ionone (CAS # 79-77-6) concluded a NOAEL of 100 mg/kg/day for maternal toxicity, based on increased salivation and marginally increased liver weights (RIFM, 2004a). The OECD 408 dietary 90-day subchronic toxicity study in rats on isomer (E)-β-ionone, in addition to the systemic endpoints, also evaluated thyroid hormones, estrous cycling, sperm parameters, and reproductive organ weights and histopathology (i.e., pituitary gland, adrenal glands, thyroid glands, parathyroid glands, oviducts/uterus/vagina, prostate gland, seminal vesicles, female mammary gland, testis, and epididymis). No effects were observed on any reproductive parameter up to the high dosage of 10,000 ppm, equivalent to 720 and 801 mg/kg/day for males and females, respectively (RIFM, 2004b). Together, these data indicate there is no concern for reproductive toxicity. The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the (E)-β-ionone NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.055 or 1818.

Additional References: Lalko et al., 2007a; Belsito et al., 2007; Oser et al., 1965; Bar and Griepentrog, 1967; Verrett et al., 1980; Prelog et al., 1951; Longenecker et al., 1939; Hartman et al., 1988; Lalko et al., 2007b; Liu et al., 2010; Vieira et al., 2011; RIFM, 2013a; Kirkpatrick et al., 2014; Willhite, 1986; Gomes-Carneiro et al., 2003; Fell et al., 1962; Ide and Toki, 1970; Bielig and Hayasida, 1940; Prelog and Meier, 1950; Lalko et al., 2007c; RIFM, 2003a; RIFM, 2004; Lalko et al., 2007d; Shillinger, 1950; Sporn et al., 1963; Sporn, 1964; Hagan et al., 1967.

Literature Search and Risk Assessment Completed on: 05/03/13.

10.1.7. Skin sensitization

Based on the available material specific data and read across to ionone (mixed isomers) (CAS # 8013-90-9); α-ionone does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available material specific data and read across to ionone (mixed isomers) (CAS # 8013-90-9; see Section 5); α-ionone does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would be expected to react with skin proteins (Roberts et al., 2007; Roberts and Natsch, 2009; OECD toolbox v3.1). However, in guinea pig test methods no results indicative of sensitization were observed to either material (Ishihara et al., 1986; Klecak et al., 1977; Klecak, 1979; Klecak, 1985; Sharp, 1978). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test to ionone (mixed isomers) (RIFM, 1972; Greif, 1967).

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/09/14.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, α-ionone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for α-ionone in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark, 1000 L mol^{-1} cm^{-1}, of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, α-ionone does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/24/15.

10.1.11. Local respiratory toxicity

The margin of exposure for α–ionone is adequate for the respiratory endpoint at the current level of use.

10.1.12. 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 acute study conducted in rats a NOAEC of 10 ppm (79 mg/m^3; the middle dose tested) was reported for the read across analog β-ionone (CAS # 14901-07-6; see Section 5) (RIFM, 2013b). At the highest dose (786.5 mg/m^3) adverse microscopic nasal lesions were seen.

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

- (79 mg/m^3) (1 m^3/1000 L) = 0.079 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/d
- (0.079 mg/L) (61.2 L/d) = 4.83 mg/d
- (4.83 mg/d)/(0.0016 kg lung weight of rat*) = 3018.75 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 2.01%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the combined inhalation exposure would be 0.186 mg/day as calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual. 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 0.287 mg/kg lung weight/day resulting in a MOE of 10518 (i.e., [3018.75 mg/kg lw/day]/[0.287 mg/kg lung weight/day]).

The MOE is significantly greater than 100. Without the adjustment for specific uncertainty factors related to inter-species and intra-species variation the material exposure by inhalation at 2.01% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd 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: RIFM, 1997; Pinching and Doving, 1974; Buchbauer et al., 1993; Isola et al., 2003a; RIFM, 2003c; Rogers et al.,

2003; RIFM, 2003b; Isola et al., 2003b; Isola et al., 2004a; Smith et al., 2004; RIFM, 2004e; Isola et al., 2004b; Rogers et al., 2005.

Literature Search and Risk Assessment Completed on: 05/03/13.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of α-ionone was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log Kow 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 (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). Following the RIFM Environmental Framework, α-ionone 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 EPISUITE ver 4.1 did identify α-ionone as being possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU (2011), α-ionone presents a risk to the aquatic compartment in the screening level assessment.

10.3. Key studies

10.3.1. Biodegradation

A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test (OECD 301 B). A biodegradation of 75.4% was observed after 28 days (RIFM, 1993).

Ecotoxicity: Not available.

Other available data:

Five studies are reported in the RIFM Database for (E) -.α.-ionone (CAS # 79-77-6).

Two 48 h *Daphnia magna* acute studies (non GLP) were conducted with test material. Under the conditions of these studies the 48-h EC50 values were 1.05 and 1.0 mg/l (RIFM, 1990a; RIFM, 1990b).

A 48 h *D. magna* acute study was conducted according to the OECD 202 guideline. The calculated EC50 at 48 h was 4.03 mg/l (RIFM, 2004).

A 96 h static system study following German standard DIN38412, Part 15 was conducted using Golden Orfe. The reported LC50 was 6.81 mg/l (RIFM, 1989a).

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.64mg/l			1,000,000	0.00264μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.504 mg/l	1.143 mg/l	1.063 mg/l			Vinyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.387 mg/l	0.973 mg/l	1.737 mg/l	10,000	0.0973μg/l	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	6.81 mg/l					
Daphnia		4.03 mg/l		1,000	4.03 μg/l	
Algae		20.9 mg/l				

Algae (*Scenedesmum subspicatus*) growth inhibition test was conducted following the German standard DIN 38412 part 9. Under the conditions of this study, the 72 h EC50 values for biomass and growth rate were 20.9 and 22.9 mg/l, respectively, and 12.2 and 21.9 mg/l at 96 h (RIFM, 1989b).

One study is reported in the RIFM Database for ionone (mixed isomers) (CAS # 8013-90-9).

A *Daphnia* immobilization static study was conducted following Guideline "Acute Toxicity for Daphnia" (C.2), Directive 92/69/EEC (1992). The EC50 was reported from the dose response curve. The reported 48 h EC50 was 5.7 mg/L (RIFM, 1999).

(E)-β-Ionone (CAS # 79-77-6) has been registered under REACH in 2010 with no additional data.

10.4. 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.

The EC50 of 4.03 mg/l Daphnia acute study for (E)-.β.-ionone was selected for PNEC calculation as it is the most conservative approach, and has also been selected in REACH registration as a key study for PNEC calculation for this group of chemical.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.29	4.29
Biodegradation factor used	1	1
Dilution factor	3	3
Regional volume of use Tonnage Band	100–1000	100–1000
Risk characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 4.03 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 05/03/13.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.12.010.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.12.010.

Appendix

Summary

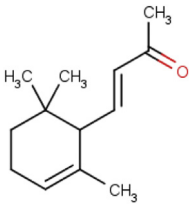
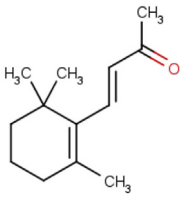
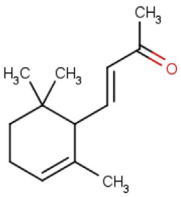
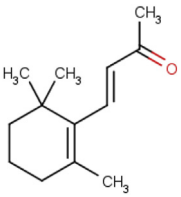
There are insufficient toxicity data on α-Ionone (RIFM # 6132, CAS # 127-41-3). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analog were calculated using EPI Suite^{TM} v4.11 developed by US EPA (USEPA, 2012)
- The 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 estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- (E)-.β.-Ionone and β-Ionone (analogs) were used as a read-across for α-Ionone (target) based on:
  - The target and analogs belong to the generic class of aliphatic ketones, specifically, ionones.
  - The target and analogs have common structural fragments of trimethyl cyclohexene and α, β unsaturated ketone.
  - The only difference is in the position of the double bond in the cyclohexene ring. The difference between structures does not essentially change physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.

	Target material	Read across material		
Principal Name	α-Ionone	(E)-.β.-Ionone	Ionone (mixed isomers)	β-Ionone
CAS No.	127-41-3	79-77-6	8013-90-9	14901-07-6
Structure				
3D Structure	http://www.thegoodscentscompany.com/opl/127-41-3.html	http://www.thegoodscentscompany.com/opl/79-77-6.html	http://www.thegoodscentscompany.com/opl/8013-90-9.html	http://www.thegoodscentscompany.com/opl/14901-07-6.html
Read-across endpoint		• Devel/Repro	• Skin sensitization	• Respiratory
Molecular Formula	C13H20O	C13H20O	C13H20O	C13H20O
Molecular Weight	192.3	192.3	192.3	192.3
Melting Point (°C, EPISUITE)	43.06	52.45	43.06	52.45
Boiling Point (°C, EPISUITE)	259.48	262.93	259.48	262.93
Vapor Pressure(Pa @ 25°C, EPISUITE)	3.626	3.026	3.626	3.026
Log Kow (KOWWIN v1.68 in EPISUITE)	4.29	4.42	4.29	4.42
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	24.67	25.16	24.67	25.16
J_{max} (mg/cm^2/h, SAM)	17.65723738	16.67928817	16.67928817	16.67928817
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	18.31956	17.620417	18.31956	17.620417
Similarity (Tanimoto score)[1]		97%	100%	97%
In silico Results for Target and Analog				
Developmental and Reproductive Toxicity				
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group		
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)		
Skin Sensitization				
Protein binding (OASIS v1.1)	• Michael addition • Michael addition >> Michael addition on conjugated systems with electron withdrawing group • Michael addition >> Michael addition on conjugated systems with electron withdrawing group >> alpha,beta-carbonyl compounds with polarized double bonds		• Michael addition • Michael addition >> Michael addition on conjugated systems with electron withdrawing group • Michael addition >> Michael addition on conjugated systems with electron withdrawing group >> alpha,beta-carbonyl compounds with polarized double bonds	
Protein binding (OECD)	• Michael addition • Michael addition >> Polarised Alkenes • Michael addition >> Polarised Alkenes >> Polarised alkene - ketones		• Michael addition • Michael addition >> Polarised Alkenes • Michael addition >> Polarised Alkenes >> Polarised alkene - ketones	
Protein binding potency (OECD)	• Highly reactive (GSH) • Highly reactive (GSH) >> 3-Alken-2-ones (MA)		• Highly reactive (GSH) • Highly reactive (GSH) >> 3-Alken-2-ones (MA)	
Protein binding alerts for skin sensitization (OASIS v1.1)	• Michael addition • Michael addition >> Michael addition on conjugated systems with electron withdrawing group • Michael addition >> Michael addition on conjugated systems with electron withdrawing group >> alpha,beta-carbonyl compounds with polarized double bonds		• Michael addition • Michael addition >> Michael addition on conjugated systems with electron withdrawing group • Michael addition >> Michael addition on conjugated systems with electron withdrawing group >> alpha,beta-carbonyl compounds with polarized double bonds	
	Sensitizer (good reliability)		Sensitizer (good reliability)	

(*continued*)

	Target material	Read across material		
Skin sensitization model (CAESAR v2.1.5)				
Metabolism				
Rat liver S9 metabolism simulator (OECD)	See Supplemental data 1	See Supplemental data 2	See Supplemental data 3	See Supplemental data 4

[1] Values calculated using Babel with FP2 fingerprint (O'Boyle et al., 2011).

- The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.

- Ionone (mixed isomers) (CAS # 8013-90-9) was identified to be a suitable read-across material based on structural similarity, reactivity, physicochemical properties, metabolism and expert judgment. α-Ionone is a component of this mixture. The only pronounced difference among the isomers in the mixture is the position of the double bond in the cyclohexene ring. The difference in the position of the double bond does not essentially change the reactivity, physicochemical properties among these isomers and therefore the toxicity profiles are expected to be similar.

Environmental analogs identified/justification

- α-Ionone is listed, in the RIFM database, as one of the 4 isomers combined in the Volume of Use survey. The others are: β-ionone (CAS # 14901-41-3), ionone (mixed isomers, CAS # 8013-90-9) and (E)-β-Ionone (CAS # 79-77-6).

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