Food and Chemical Toxicology 144 (2020) 111542

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

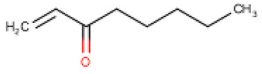
Short Review

RIFM fragrance ingredient safety assessment, 1-octen-3-one, CAS Registry Number 4312-99-6

A.M. Api [a], F. Belmonte [a], D. Belsito [b], S. Biserta [a], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M.A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], S. Gadhia [a], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], D.C. Liebler [i], M. Na [a], D. O'Brien [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], F. Rodriguez-Ropero [a], J. Romine [a], N. Sadekar [a], D. Salvito [a], T.W. Schultz [k], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677 USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 010719. This version replaces any previous versions.



Name: 1-Octen-3-one
CAS Registry Number: 4312-99-6

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., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration

(*continued on next column*)

(*continued*)

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2020.111542
Received 6 August 2019; Received in revised form 16 March 2020; Accepted 19 June 2020
Available online 5 July 2020

(*continued*)

NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

1-Octen-3-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-octen-3-one is not genotoxic. Data on 1-penten-3-one (CAS # 1629-58-9) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. The developmental and local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class III material, and the exposure to 1-octen-3-one is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 1-octen-3-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-octen-3-one was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2015; RIFM, 2011a)
Repeated Dose Toxicity: NOAEL = 7.95 mg/kg/day.	Morgan (2001)
Reproductive Toxicity: Developmental toxicity: No NOAEL available. Exposure is below the TTC. Fertility: NOAEL = 8 mg/kg/day.	Morgan (2001)
Skin Sensitization: Not a sensitization concern; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 3.1 (BIOWIN 3)	(EPI Suite v.4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 17.1 L/kg	(EPI Suite v.4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 93.2 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 93.2 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.0932 μg/L

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

(*continued on next column*)

(*continued*)

1. Identification

1. **Chemical Name:** 1-Octen-3-one
2. **CAS Registry Number:** 4312-99-6
3. **Synonyms:** Amyl vinyl ketone; Vinyl amyl ketone; Oct-1-en-3-one; 1-Octen-3-one
4. **Molecular Formula:** $C_8H_{14}O$
5. **Molecular Weight:** 126.19
6. **RIFM Number:** 1280
7. **Stereochemistry:** Isomer not specified. One geometric center present and 2 isomers possible.

2. Physical data

1. **Boiling Point:** 60 °C @ 16 mm Hg (Fragrance Materials Association [FMA] Database), 161.99 °C (EPI Suite)
2. **Flash Point:** 63 °C (Globally Harmonized System), 145 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.10 (Biobyte Corp.), 2.37 (EPI Suite)
4. **Melting Point**: −32.07 °C (EPI Suite)
5. **Water Solubility:** 895.4 mg/L (EPI Suite)
6. **Specific Gravity:** 0.87 (FMA Database)
7. **Vapor Pressure:** 3.01 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** <0.1 metric ton per year (IFRA, 2015)
2. **95th Percentile Concentration in Shampoo:** 0.0000056% (RIFM, 2017) No reported use in hydroalcoholics
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0000001 mg/kg/day (RIFM, 2017)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 1-Penten-3-one (CAS # 1629-58-9)
   c. **Reproductive Toxicity:** 1-Penten-3-one (CAS # 1629-58-9)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment. Additional References: None.

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

1-Octen-3-one is not reported to occur in foods by the VCF*:

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

8. REACH dossier

Pre-registered for 2010; no dossier available as of 03/13/20.

9. Conclusion

The existing information supports the use of this materials as described in this safety assessment.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1-octen-3-one does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 1-octen-3-one has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with a modified OECD TG 471 (only 1 test strain was used in the standard plate incorporation method). *Salmonella typhimurium* strain TA100 was treated with 1-octen-3-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate (purity: 98.4%). It was concluded that 1-octen-3-one induced mutation in the histidine-requiring strain TA100 of *Salmonella typhimurium* when tested under the conditions of this study. These conditions included treatments at concentrations up to at least 500 μg/plate (toxic concentration) in the presence and absence of a rat liver metabolic activation system (S9) (RIFM, 2013). Under the conditions of the study, 1-octen-3-one was mutagenic in the Ames test.

The mutagenic activity of 1-octen-3-one 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 1-octen-3-one in DMSO at concentrations up to 5000 μg/plate (purity: >97%). Small but statistically significant increases in revertant numbers were observed following 1-octen-3-one treatments of strain TA100 both in the presence and absence of S9 metabolic activation. This weak mutagenic response was not reproduced on every experimental occasion, but where significant increases were observed, they were always small in magnitude and limited by toxicity at the next highest 1-octen-3-one concentrations. It was concluded that 1-octen-3-one induced mutations in TA100 when tested up to toxic concentrations in the presence and absence of a rat liver metabolic activation system (S9) (RIFM, 2009). Under the conditions of the study, 1-octen-3-one was mutagenic in the Ames test.

A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476/GLP guidelines. Mouse lymphoma cells were treated with 1-octen-3-one in DMSO at concentrations up to 1262 μg/mL (purity: 98.3%). Effects were evaluated both with and without metabolic activation for 3 h and for 24 h without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2011b). Under the conditions of the study, 1-octen-3-one was not mutagenic to mammalian cells *in vitro*.

Due to the discrepancies in the *in vitro* data between bacterial cells and mammalian cells, in addition to the weak responses observed in the Ames assay, an *in vivo* Comet assay was conducted to clarify the responses. Additionally, an *in vivo* Comet was conducted in compliance with GLP regulations. 1-Octen-3-one was administered in corn oil via oral gavage to groups of male Han Wistar rats (6/sex/dose). Doses of 45, 90, and 180 mg/kg were administered (purity: 98.1%). Rats from each dose level were euthanized at the end of the study, and liver tissue was analyzed for tail intensity (percent DNA in tail) and tail migration in the Comet assay. Following treatment with 1-octen-3-one at all dose levels, no increases in the group mean tail intensity and tail moment values were observed when compared to the vehicle control group (RIFM, 2015). Under the conditions of the study, 1-octen-3-one did not induce DNA damage in the liver of male rats in the Comet assay *in vivo*.

The clastogenic activity of 1-octen-3-one was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 1-octen-3-one in DMSO at concentrations up to 1262 μg/mL in the dose range (DRF) study; micronuclei analysis was conducted at 15 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h (purity: 98.3%). 1-Octen-3-one did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2011a). Under the conditions of the study, 1-octen-3-one was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the weight of evidence presented, 1-octen-3-one does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/06/18.

10.1.2. Repeated dose toxicity

The MOE for 1-octen-3-one is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 1-octen-3-one. Read-across material 1-penten-3-one (CAS # 1629-58-9; see Section V) has sufficient data that can be used to support the repeated dose toxicity endpoint. The National Toxicology Program conducted subchronic toxicity studies in both male and female F344 rats and B6C3F1 mice. Groups of rats and mice (10/sex/species/concentration) were exposed to 0, 2, 4, or 8 ppm 1-penten-3-one (purity: 90.5%) by inhalation 6 h per day, 5 days per week, for 13 weeks. No treatment-related mortalities were reported in rats or mice of either sex. The nasal cavity was the major target organ of 1-penten-3-one in both rats and mice, and rats were more susceptible to respiratory tract toxicity than mice. Body weights of animals exposed to 1-penten-3-one (4 and 8 ppm) were significantly reduced, subsequently affecting the absolute weight of several organs, such as heart, kidney, liver, and lung. In rats, the relative organ weights of kidney and liver were increased at 8 ppm; a similar effect was observed in male rats in the 4 ppm group. Relative lung weights were significantly increased in male rats while absolute lung weights were decreased in female rats receiving 8 ppm. Histopathology revealed significant treatment-related lesions only in the nose and lungs of the treated rats. At week 13, exposure to 1-penten-3-one resulted in a concentration-related increased incidence and severity of olfactory epithelial necrosis, regeneration, and slight respiratory metaplasia of the nasal cavity. Olfactory epithelial necrosis was the most prominent along the dorsal meatus and associated turbinates. Necrotic lesions were also reported in rats exposed to high concentrations of 1-penten-3-one. At 2 ppm, only the respiratory epithelium was affected in rats, with male rats being more sensitive to the effects of 1-penten-3-one in the nasal cavity. At the highest exposure concentration, increased incidences of chronic interstitial inflammation were reported in rat lungs, which was characterized by the thickening of the alveolar wall. Since no significant systemic toxicity was observed at the highest dose, a NOAEL of 8 ppm was considered for the repeated dose toxicity. All the reported effects of lungs and nasal cavity were considered as local effects. In mice, although the absolute weights of heart, kidney, liver, and lung were decreased, only the relative kidney weights were significantly decreased in male mice exposed to 8 ppm. With an exception of mild leukopenia in female mice, all hematology parameters were within historical limits. Treatment-related lesions were identified in the nose, larynx, lung, and kidney. Exposure to 1-penten-3-one for 13 weeks resulted in a concentration-related increase in the incidence and severity of olfactory epithelial atrophy and respiratory metaplasia. Unlike rats, necrosis was not observed in mice. In both male and female mice, exposure to 4 or 8 ppm was associated with an eosinophilic proteinaceous exudation often containing inflammatory cells. Nasal lesions were apparent in animals exposed to 2 ppm with minimal squamous metaplasia. Overall, female mice appeared slightly more sensitive to the nasal effects of 1-penten-3-one. In male and female mice exposed to 8 ppm, sections of the larynges were also recognized as having potential treatment-related lesions of minimal squamous hyperplasia along the base of the epiglottis and along the lateral walls of the arytenoid cartilage. Treatment-related increased infiltration of peribronchial lymphocytes was noted in the lungs of male (8 ppm) and female (4 and 8 ppm) mice. The kidneys of untreated male B6C3F1 mice typically exhibit a clear cytoplasmic vacuolization of renal tubule epithelium in the middle to outer cortex. This vacuolization was decreased or absent altogether in kidneys of male mice exposed to 8 ppm. Hence, a NOAEL of 8 ppm was established from the study. Using standard minute volume and body weight values for male and female F344 rats and B6C3F1 mice, the calculated NOAEL for effects on repeated dose toxicity is 7.95 mg/kg/day for rats and 11.88 mg/kg/day for mice (Morgan, 2001).

Therefore, the 1-octen-3-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1-penten-3-one NOAEL in mg/kg/day by the total systemic exposure to 1-octen-3-one, 7.95/0.0000001 or 79500000.

In addition, the total systemic exposure to 1-octen-3-one (0.0001 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/04/19.

10.1.3. Reproductive toxicity

There are no developmental toxicity data on 1-octen-3-one or on any read-across materials. The total systemic exposure to 1-octen-3-one is below the TTC for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

The MOE for 1-octen-3-one is adequate for the fertility endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 1-octen-3-one or on any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 1-octen-3-one (0.0001 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

There are no fertility data on 1-octen-3-one. Read-across material 1-penten-3-one (CAS # 1629-58-9; see Section V) has sufficient fertility data that can be used to support the fertility endpoint. The National Toxicology Program conducted subchronic toxicity studies in both male and female F344 rats and B6C3F1 mice. Groups of rats and mice (10/sex/species/concentration) were exposed to 0, 2, 4, or 8 ppm 1-penten-3-one (purity: 90.5%) 6 h per day, 5 days per week, for 13 weeks. The nasal cavity was the major target organ of EVK in both rats and mice, and rats were more susceptible to respiratory tract toxicity than mice. In addition to systemic toxicity parameters, sperm motility and vaginal cytology were also evaluated. There were no significant effects on sperm motility or vaginal cytology in rats or mice; therefore, the NOAEL for fertility was considered to be 8 ppm, the highest dose tested. Using standard minute volume and body weight values for male and female F344 rats and B6C3F1 mice, the calculated NOAEL for effects on fertility is 8 mg/kg/day for rats and 12 mg/kg/day for mice. The most conservative NOAEL of 8 mg/kg/day from rats was selected for the fertility endpoint (Morgan, 2001).

Therefore, the 1-octen-3-one MOE for the fertility endpoint can be calculated by dividing the 1-penten-3-one NOAEL in mg/kg/day by the total systemic exposure to 1-octen-3-one, 8/0.0000001 or 80000000.

In addition, the total systemic exposure to 1-octen-3-one (0.0001 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: RIFM, 1974.

Literature Search and Risk Assessment Completed On: 01/02/19.

10.1.4. Skin sensitization

Based on the existing data and the application of DST, 1-octen-3-one does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for 1-octen-3-one. Acting conservatively due to the absence of data the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 1-octen-3-one that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable

Table 1
Maximum acceptable concentrations for 1-octen-3-one that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.005%	NRU[b]
2	Products applied to the axillae	0.001%	NRU[b]
3	Products applied to the face using fingertips	0.029%	NRU[b]
4	Fine fragrance products	0.027%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.007%	NRU[b]
6	Products with oral and lip exposure	0.016%	5.6×10^{-6}%
7	Products applied to the hair with some hand contact	0.056%	NRU[b]
8	Products with significant ano-genital exposure	0.003%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	9.6×10^{-7}%
10	Household care products with mostly hand contact	0.192%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.107%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	NRU[b]

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/06/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, 1-octen-3-one would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 1-octen-3-one in experimental models. UV absorption spectra indicate no absorption between 290 and 500 nm. As such, it is not a concern for phototoxicity or photoallergenicity (Henry, 2009). Based on the lack of absorbance, 1-octen-3-one does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–500 nm. As the material does not absorb in the range of interest, it is not a concern for phototoxicity or photoallergenicity (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-octen-3-one is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 1-octen-3-one. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 4700 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Morgan (2001).

Literature Search and Risk Assessment Completed On: 12/12/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1-octen-3-one was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1-octen-3-one was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 1-octen-3-one as not possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 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 $\geq$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).

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 1-octen-3-one does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. 1-Octen-3-one has been pre-registered for REACH with no additional data at this time.

10.2.2. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.1	2.1
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	Not reported
Risk Characterization: PEC/PNEC	**<1**	**N/A**

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

The RIFM PNEC is 0.0932 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/10/18.

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/

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 05/30/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111542.

Appendix

Read-across Justification

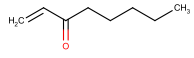
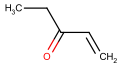
Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	93.2			1000000	0.0932	

(OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	1-Octen-3-one	1-Penten-3-one
CAS No.	4312-99-6	1629-58-9
Structure		
Similarity (Tanimoto Score)		0.58
Read-across Endpoint		• Repeated dose • Fertility
Molecular Formula	$C_8H_{14}O$	C_5H_8O
Molecular Weight	126.19	84.11
Melting Point (°C, EPI Suite)	−32.07	−69.06
Boiling Point (°C, EPI Suite)	161.99	93.22
Vapor Pressure (Pa @ 25 °C, EPI Suite)	401	5.09E+003
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.37	0.90
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	895.4	2.19e+004
J_{max} (μg/cm^2/h, SAM)	57.98	625.09
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.22E+000	3.52E+000
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (moderate reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 1-octen-3-one (CAS # 4312-99-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 1-penten-3-one (CAS # 1629-58-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 1-Penten-3-one (CAS # 1629-58-9) was used as a read-across analog for the target material 1-octen-3-one (CAS # 4312-99-6) for the repeated dose and fertility endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated straight chain ketones.
  - The target material and the read-across analog share an α,β-unsaturated straight chain ketone structure.
  - The key difference between the target material and the read-across analog is that while the target material is a C8 straight chain the read-across analog is a C5 straight chain. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Morgan, D.L., Ward, S.M., Wilson, R.E., Price, H.C., O'Conner, R.W., Seely, J.C., Cunningham, M.L., 2001. Inhalation toxicity studies of the alpha,beta-unsaturated ketones: ethyl vinyl ketone. Inhal. Toxicol. 13 (8), 633–658.

OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974. 90-Day Feeding Study in Rats with 1-Octen-3-One. Private Communication to FEMA. Unpublished report from Cox, G.E., Bailey, D.E. & Morgareidge, K. RIFM report number 21033. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Oct-1-en-3-one: Reverse Mutation in Five Histidine-Requiring Strains of Salmonella typhimurium. Unpublished report from Beevers, C. RIFM report number 73538. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011a. Oct-1-en-3-one: Induction of Micronuclei in Cultured Human Peripheral Blood Lymphocytes. Unpublished report from Lloyd, M. RIFM report number 73540. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011b. Oct-1-en-3-one: Mutation at the Hprt Locus of Mouse Lymphoma L5178Y Cells (MLA) Using the MicrotitreR Fluctuation Technique. Unpublished report from Lloyd, M. RIFM report number 73541. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Oct-1-en-3-one: Investigation into the Mechanism of Mutagenicity: Reverse Mutation in One Histidine-Requiring Strain of Salmonella typhimurium. Unpublished report from Bowen, R. RIFM report number 73539. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. 1-Octen-3-one: Rat Alkaline Comet Assay. Unpublished report from Keig-Shevlin, Z. RIFM report number 73575. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Exposure Survey 17. August 2017.

Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015b. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.

Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.

Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

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

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