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RIFM fragrance ingredient safety assessment, tetrahydro-pseudo-ionone, CAS Registry Number 1322-58-3

A.M. Api [a], D. Belsito [b], 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], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member 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 Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member 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 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 Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member 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 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*

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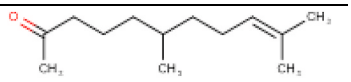

Name: Tetrahydro-pseudo-ionone
CAS Registry Number: 1322-58-3
Additional CAS Numbers:

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(*continued*)

4433-36-7
3,4,5,6-Tetrahydropseudoionone (No reported use)
*Included because the materials are isomers.

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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

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BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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.

Tetrahydro-pseudo-ionone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tetrahydro-pseudo-ionone is not genotoxic. Data from read-across analog 2,4,4,7-tetramethyl-6-octen-3-one (CAS # 74338-72-0) provided a MOE > 100 for the repeated dose toxicity endpoint. Data from read-across analog 6-methylhept-5-en-2-one (CAS # 110-93-0) provided a MOE > 100 for the reproductive toxicity endpoint. Data from tetrahydro-pseudo-ionone (with weight of evidence data from read-across analog 11-tridecen-6-one, 8,12-dimethyl-; CAS # 68141-18-4) provided a NESIL of 9400 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and the exposure to tetrahydro-pseudo-ionone is below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; tetrahydro-pseudo-ionone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, tetrahydro-pseudo-ionone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2015a; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (1996)
Reproductive Toxicity: NOAEL = 200 mg/kg/day.	(RIFM, 2002b; RIFM, 2002c)
Skin Sensitization: NESIL = 9400 μg/cm^2.	RIFM (1988)
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: Critical Measured Value: 34% (OECD 301D) for CAS # 4433-36-7	RIFM (1999)
Bioaccumulation: Screening-level: 397 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2.0 mg/L	(RIFM Framework; Salvito et al., 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 et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 2.0 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 2.0 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe Not applicable; cleared at the screening-level	

1. Identification

Chemical Name: Tetrahydro-pseudo-ionone	**Chemical Name**: 3,4,5,6-Tetrahydropseudoionone
CAS Registry Number: 1322-58-3	**CAS Registry Number:** 4433-36-7
Synonyms: 6,10-Dimethylundecen-2-one; Undecen-2-one, 6,10-dimethyl-; 6,10-Dimethylundec-3-en-2-one; Tetrahydro-pseudo-ionone	**Synonyms:** 3,4,5,6-Tetrahydropseudoionone; 6,10-Dimethyl-9-undecen-2-one; 6,10-Dimethylundec-9-en-2-one; 9-Undecen-2-one, 6,10-dimethyl-; Citronellylacetone; Dihydrogeranylacetone; Tetrahydro pseudo ionone; Tetrahydropseudoionone
Molecular Formula: $C_{13}H_{24}O$	**Molecular Formula:** $C_{13}H_{24}O$
Molecular Weight: 196.33	**Molecular Weight:** 196.33
RIFM Number: 5234	**RIFM Number:** N/A
Stereochemistry: Isomer not specified. One stereocenter and 2 stereoisomers possible.	**Stereochemistry:** Isomer not specified. One stereocenter and 2 stereoisomers possible.

2. Physical data*

1. **Boiling Point:** 250.01 °C (EPI Suite)
2. **Flash Point:** >93 °C (GHS)
3. **Log K_{OW}:** 4.44 (EPI Suite)
4. **Melting Point**: 5.66 °C (EPI Suite)
5. **Water Solubility:** 7.324 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.0285 mm Hg @ 20 °C (EPI Suite v4.0), 0.0441 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

*Physical data for both materials are identical.

3. Volume of use (worldwide band)

1. 0.1–1 metric tons per year (IFRA, 2015)

4. Exposure*** to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.1) ***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.11% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00033 mg/kg/day or 0.0031 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.0032 mg/kg/day (RIFM, 2020b)

*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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; 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 or 97.5th percentile, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate* (Expert Judgment)

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 2,4,4,7-Tetramethyl-6-octen-3-one (CAS # 74338-72-0)
   c. **Reproductive Toxicity:** 6-Methylhept-5-en-2-one (CAS # 110-93-0)
   d. **Skin Sensitization:** 11-Tridecen-6-one, 8,12-dimethyl- (CAS # 68141-18-4) (Weight of evidence material)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Tetrahydro-pseudo-ionone and 3,4,5,6-tetrahydropseudoionone are not reported to occur in food by the VCF.*

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

9. REACH dossier

Tetrahydro-pseudo-ionone is pre-registered for 2010, no dossier available as of 10/09/20. Dossier available for 3,4,5,6-tetrahydropseudoionone; accessed 10/09/20 (ECHA, 2016).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for tetrahydro-pseudo-ionone are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.72
2	Products applied to the axillae	0.22
3	Products applied to the face/body using fingertips	4.3
4	Products related to fine fragrances	4.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.0
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	1.0
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.0
5D	Baby cream, oil, talc	0.33
6	Products with oral and lip exposure	1.0
7	Products applied to the hair with some hand contact	5.1
8	Products with significant ano-genital exposure (tampon)	0.33
9	Products with body and hand exposure, primarily rinse-off (bar soap)	7.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.1
10B	Aerosol air freshener	28
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.33
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

tetrahydro-pseudo-ionone, the basis was the reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 9400 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, tetrahydro-pseudo-ionone does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Tetrahydro-pseudo-ionone was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of tetrahydro-pseudo-ionone 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 tetrahydro-pseudo-ionone in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, tetrahydro-pseudo-ionone was not mutagenic in the Ames test.

The clastogenic activity of tetrahydro-pseudo-ionone 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 tetrahydro-pseudo-ionone in DMSO at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Tetrahydro-pseudo-ionone did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015b). Under the conditions of the study, tetrahydro-pseudo-ionone was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, tetrahydro-pseudo-ionone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data for tetrahydro-pseudo-ionone. Read-across material, 2,4,4,7-tetramethyl-6-octen-3-one (CAS # 74338-72-0; see Section VI) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint.

An OECD 407/GLP oral gavage 28-day toxicity study was conducted in Sprague Dawley rats. Groups of 5 rats/sex/dose were administered 2,4,4,7-tetramethyl-6-octen-3-one daily via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day for 28 days. The liver weights among both high-dose males and females were statistically significantly increased, and higher kidney weights were also observed in male rats of the high-dose group. Enlarged and discolored livers in both sexes (4 males and 1 female) and enlarged kidneys in males were observed at necropsy in the highest dose group. Correspondingly, centrilobular hepatocellular hypertrophy was observed among animals of the high-dose group during histopathological evaluation. In the kidneys of some males dosed at 200 and 1000 mg/kg/day, an increase in the severity of hyaline droplet formation in the cortical tubules, accompanied by minimal to moderate granular cast formation, medullary tubule dilation, and tubular basophilia indicated α-2u-globulin nephropathy. The authors of the study report determined the NOAEL to be 50 mg/kg/day. However, these kidney changes were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992 and Lehman-McKeeman et al., 1990). The liver weight increases can be considered to be adaptive as there was a lack of histopathological evidence of liver cell damage and clinical chemistry alterations (Hall et al., 2012). Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1996).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3, or 333 mg/kg/day.

Therefore, the tetrahydro-pseudo-ionone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,4,4,7-tetramethyl-6-octen-3-one NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-pseudo-ionone, 333/0.0032, or 104063.

In addition, the total systemic exposure to tetrahydro-pseudo-ionone (3.2 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/16/20.

11.1.3. Reproductive toxicity

The margin of exposure for tetrahydro-pseudo-ionone is adequate for the developmental and fertility endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data for tetrahydro-pseudo-ionone. Read-across material, 6-methylhept-5-en-2-one (CAS # 110-93-0; see Section VI) has sufficient developmental toxicity data to support the developmental toxicity endpoint. An OECD 414/GLP oral gavage prenatal developmental toxicity study was conducted in Wistar rats. Groups of 25 time-mated female rats/dose were administered 6-methylhept-5-en-2-one (methylheptenon) via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day in olive oil on day 6–19 post coitum (p.c.). At 1000 mg/kg/day, there was a statistically significant decrease in food consumption (7%) when compared to the control group. A statistically significant reduction in bodyweight gain was also observed in the high-dose group animals (14%) when compared to the control group for day 6–19 p.c., along with a statistically significant decrease in the corrected bodyweight gain (29% below the controls). The placental and fetal body weights were statistically significantly decreased (13% and 9% below the controls, respectively). The rates of fetuses/litters with certain skeletal variations (i.e., delays in the ossification of parts of the skull, vertebral column, and sternum) were significantly increased for the high-dose group dams. There were signs of maternal toxicity at 1000 mg/kg/day, predominantly substantiated by adverse clinical findings (i.e., transient occurrences of

abdominal position, unsteady gait, and/or ataxia) and statistically significant impairments in food consumption and bodyweight gains. However, there were no treatment-related adverse effects on the gestational parameters up to the highest dose level. Conception rate, the mean number of corpora lutea, total implantations, resorptions, and live fetuses, fetal sex ratio, or pre- and post-implantation losses were not affected by treatment. The mean placental and fetal body weights were statistically significantly reduced (13% and 9% below the controls, respectively). Correspondingly, the rates for certain skeletal variations were statistically significantly increased and outside historical control ranges. Thus, the NOAEL for maternal and prenatal developmental toxicity was considered to be 200 mg/kg/day, based on decreased placental and fetal body weights and increased skeletal variations observed at the highest dose group (RIFM, 2002b).

Therefore, the tetrahydro-pseudo-ionone MOE for the developmental toxicity endpoint can be calculated by dividing the 6-methylhept-5-en-2-one NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-pseudo-ionone, 200/0.0032, or 62500.

There are no fertility data for 6,10-dimethylundeca-5,9-dien-2-one. Read-across material, 6-methylhept-5-en-2-one (CAS # 110-93-0; see Section VI) has sufficient fertility data to support the fertility endpoint. An OECD 408/GLP oral gavage 90-day subchronic study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered 6-methylhept-5-en-2-one (methylheptenon) via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day in olive oil for 13 weeks. In addition to systemic toxicity parameters, estrous cycle assessment of all females and sperm parameters from all males were evaluated. Vaginal smears for estrous cycle determination among the female animals were prepared and evaluated each day during the last 4 weeks of the study. At 1000 mg/kg/day, there was a statistically significant reduction in spermatozoa in the cauda epididymis and spermatids in the testis, with an increase in morphologically abnormal sperm in 3 out of 10 males. Furthermore, 3 high-dose group male rats revealed extreme diffuse atrophy of the testes, which was associated with aspermia and luminal debris in the epididymides, and 2 other male rats experienced minimal to slight focal tubular atrophy in the testes. There were no treatment-related adverse effects on estrous cycle determinations conducted from days 63–91. Thus, the NOAEL for reproductive toxicity was considered to be 200 mg/kg/day, based on testicular toxicity affecting spermatogenesis among males of the high-dose group (RIFM, 2002c).

Therefore, the tetrahydro-pseudo-ionone MOE for the fertility endpoint can be calculated by dividing the 6-methylhept-5-en-2-one NOAEL in mg/kg/day by the total systemic exposure to tetrahydro-pseudo-ionone, 200/0.0032, or 62500.

In addition, the total systemic exposure to tetrahydro-pseudo-ionone (3.2 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1.1. Derivation of reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020c) and a reference dose of 200 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for tetrahydro-pseudo-ionone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.1.4. Skin sensitization

	Skin Sensitization
Step 1: Data	**Sufficient**
Step 2: Read-across	
Step 3: DST	
Step 4: Generate data	
NESIL	9400 μg/cm^2

Based on the existing data and weight of evidence analog 11-tridecen-6-one, 8,12-dimethyl- (CAS # 68141-18-4), tetrahydro-pseudo-ionone is considered a skin sensitizer with a defined NESIL of 9400 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data and weight of evidence analog 11-tridecen-6-one, 8,12-dimethyl- (CAS # 68141-18-4; see Section VI), tetrahydro-pseudo-ionone is considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.2). In a murine Local Lymph Node Assay (LLNA), the weight of evidence analog 11-tridecen-6-one, 8,12-dimethyl- was found to be sensitizing with an EC3 value of 34.1% (8525 μg/cm^2) (RIFM, 2002a). In human maximization tests, skin sensitization reactions were present in 2 studies and absent in 1 study with 8% (5520 μg/cm^2) tetrahydro-pseudo-ionone in petrolatum (RIFM, 1982; RIFM, 1977; RIFM, 1978). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 9448 μg/cm2 of tetrahydro-pseudo-ionone in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 106 volunteers (RIFM, 1988).

Based on the weight of evidence from structural analysis, human studies, and weight of evidence, analog 11-tridecen-6-one, 8,12-dimethyl-, tetrahydro-pseudo-ionone is considered a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 9400 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020c) and a reference dose of 2 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, tetrahydro-pseudo-ionone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for tetrahydro-pseudo-ionone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, tetrahydro-pseudo-ionone does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

Table 1
Data summary for tetrahydro-pseudo-ionone and weight of evidence analog, 11-tridecen-6-one, 8,12-dimethyl-.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction)μg/cm^2	NOEL-HMT (induction)μg/cm^2	LOEL[b] (induction)μg/cm^2	WoE NESIL[c] μg/cm^2
8525 [1]	Weak	9448	N/A	5520	9400

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level for tetrahydro-pseudo-ionone is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on tetrahydro-pseudo-ionone. Based on the Creme RIFM Model, the inhalation exposure is 0.0031 mg/day. This exposure is 151.6 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of tetrahydro-pseudo-ionone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, tetrahydro-pseudo-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 EPI Suite v4.11 (US EPA, 2012a) identified tetrahydro-pseudo-ionone as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), tetrahydro-pseudo-ionone does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.1.1. Biodegradation. For CAS # 4433-36-7.

RIFM, 1999: The ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. Under the conditions of the study, biodegradation of 34% was observed after 28 days.

11.2.1.1.2. Ecotoxicity. For CAS # 4433-36-7.

RIFM, 2000: A *Daphnia magna* acute toxicity study was conducted according to the Council Directive 92/69/EEC C.1 method under static conditions. The geometric mean EC 0/EC 100 after 48 h of exposure based on nominal concentration was reported to be 4 mg/L nominal concentration.

11.2.1.2. Other available data. Tetrahydro-pseudo-ionone has been registered for REACH with no additional data at this time.

11.2.2. Risk assessment refinement

Since tetrahydro-pseudo-ionone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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 Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.4	4.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

*Combined Regional VoU for all CAS #s.

The RIFM PNEC is 2.0 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level and

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1)**	2.0			1,000,000	0.0020	

therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/06/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

12.1. 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 05/11/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112449.

Appendix

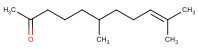
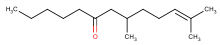
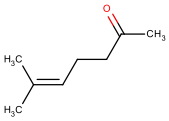
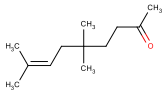
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), 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, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Tetrahydro-pseudo-ionone	11-Tridecen-6-one, 8,12-dimethyl-	6-Methyl-5-hepten-2-one	5,5,8-Trimethyl-7-nonen-2-one
CAS No.	1322-58-3	68141-18-4	110-93-0	74338-72-0
Structure				
Similarity (Tanimoto Score)		0.58	0.54	0.36
Endpoint		Skin sensitization	Developmental toxicity	Repeated dose toxicity
Molecular Formula	$C_{13}H_{24}O$	$C_{15}H_{28}O$	$C_8H_{14}O$	$C_{12}H_{22}O$
Molecular Weight	196.33	224.39	126.20	182.31
Melting Point (°C, EPI Suite)	5.66	26.62	−67.10	1.35
Boiling Point (°C, EPI Suite)	250.01	283.19	173.50	224.71
Vapor Pressure (Pa @ 25 °C, EPI Suite)	5.88	1.08	237.31	20.93
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	7.32	0.76	1651.00	24.33
Log K_{OW}	4.44	5.43	2.06	3.91
J_{max} (μg/cm2/h, SAM)	0.99	0.12	70.42	2.81
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	88.66	156.04	21.48	66.77
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized	Not categorized	Not categorized	Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on tetrahydro-pseudo-ionone (CAS # 1322-58-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 6-methyl-5-hepten-2-one (CAS # 110-93-0), 11-tridecen-6-one, 8,12-dimethyl- (CAS # 68141-18-4), and 5,5,8-trimethyl-7-nonen-2-one (CAS # 74338-72-0) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 6-Methyl-5-hepten-2-one (CAS # 110-93-0) was used as a read-across analog for the target material tetrahydro-pseudo-ionone (CAS # 1322-58-3) for the reproductive toxicity endpoint.
  The target substance and the read-across analog are structurally similar and belong to the class of aliphatic branched-chain ketones.
  The target substance and the read-across analog share similar unsaturated, branched structures.
  The key structural difference between the target substance and the read-across analog is the target substance has a dimethyl-substituted C11 aliphatic chain, whereas the read-across analog has a monomethyl C7 aliphatic chain. The target has a double bond at the tenth position, whereas the read-across analog has a double bond at the fifth position. These structural differences are toxicologically insignificant.
  Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these unsaturated, branched ketone structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  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. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  The target substance 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.
- 5,5,8-Trimethyl-7-nonen-2-one (CAS # 74338-72-0) was used as a read-across analog for the target material tetrahydro-pseudo-ionone (CAS # 1322-58-3) for the repeated dose toxicity endpoint.
  The target substance and the read-across analog are structurally similar and belong to the class of aliphatic branched-chain ketones.
  The target substance and the read-across analog share similar unsaturated, branched structures.
  The key structural difference between the target substance and the read-across analog is the target substance has a dimethyl-substituted C11 aliphatic chain, whereas the read-across analog has a trimethyl-substituted C9 aliphatic chain. The target has a double bond at the tenth position, whereas the read-across analog has a double bond at the seventh position. These structural differences are toxicologically insignificant.
  Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these unsaturated, branched ketone structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  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. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  The target substance 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.
- 11-Tridecen-6-one, 8,12-dimethyl- (CAS # 68141-18-4) was used as a weight of evidence material for the target material tetrahydro-pseudo-ionone (CAS # 1322-58-3) for the skin sensitization endpoint.
  The target substance and the weight of evidence material are structurally similar and belong to the class of aliphatic, branched-chain ketones.
  The target substance and the weight of evidence material share similar unsaturated, branched structures.
  The key structural differences between the target substance and the weight of evidence material are that the target substance has a trimethyl C10 aliphatic chain with a ketone at the 2 position, whereas the weight of evidence material has a dimethyl C13 aliphatic chain with the ketone at the 6 position. Moreover, the target has a double bond at the tenth position, whereas the read-across analog has a double bond at the eleventh position. These structural differences are toxicologically insignificant.
  Structural similarity between the target substance and the weight of evidence material is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these unsaturated, branched structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  The physical–chemical properties of the target substance and the weight of evidence material 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 substance and the weight of evidence material.
  The target substance and the weight of evidence material 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 weight of evidence material and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, divalent S? **No**

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene (see explanation in Cramer et al., 1978)? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **Yes**
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? **Yes**
Q21. 3 or more different functional groups? **No**
Q18. One of the following categories? (a) a vicinal diketone; or a ketone or ketal of a ketone attached to a terminal vinyl group (b) a secondary alcohol or ester of a secondary alcohol attached to a terminal vinyl group (c) allyl alcohol or its acetal, ketal, or ester derivative (d) allyl mercaptan, an allyl sulfide, an allyl thioester or allylamine (e) acrolein, a methacrolein or the acetals (f) acrylic or methacrylic acid (g) an acetylenic compound (h) an acyclic aliphatic ketone, ketal or keto-alcohol with no other functional groups and with 4 or more carbons on either side of the keto group (i) a substance in which the functional groups are all sterically hindered (see Cramer et al., 1978 for detailed explanation)? **Yes, Intermediate Class II**

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