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Short Review

RIFM natural complex substance (NCS) fragrance ingredient safety assessment, petitgrain mandarin oil, CAS registry number 8014-17-3, RIFM ID: 250-E2.12

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ARTICLE INFO

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1. Natural complex substance (NCS) identification

Petitgrain mandarin oil, CAS registry number 8014-17-3, RIFM ID: 250-E2.12. See Table 1 for Substance Identification and Table 2 for Additional Information.

2. Summary

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

Petitgrain mandarin oil was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data for components of the NCS do not show a concern for genotoxicity. Petitgrain mandarin oil was evaluated for the repeated dose and reproductive toxicity endpoints on the basis of component analysis using a combination of target data, read-across data, and TTC. Petitgrain mandarin oil is safe for use under the conditions described in this safety assessment for the repeated dose and reproductive toxicity endpoints. Data for components of the NCS do not show a concern for skin sensitization under the current, declared levels of use. The photoirritation endpoint was evaluated based on UV/Vis absorption spectra and *in vivo* study data; Petitgrain mandarin oil is not a concern for

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Table 1
NCS identification.

NCS	Synonyms
NCS Name: Petitgrain mandarin oil **CAS #** 8014-17-3 **RIFM ID:** 250-E2.12 **Percent Composition Known:** 100% **Family:** Rutaceae **Genus:** Citrus **Botanical Definition:** Leaf/Twig **Processing Method:** Essential oil by steam distillation	*Citrus aurantium* *Citrus nobilis* Lour. *Citrus reticulata* *Citrus reticulata* Blanco *Citrus reticulata* Blanco mandarin oil *Citrus reticulata* leaf oil Mandarin orange, extract Petitgrain mandarin oil Rutaceae ﾌﾟﾁｸﾞﾚﾝ (*Citrus* spp.) 油

photoirritation based on the current, declared levels of use. The photoallergenicity endpoint was evaluated based on *in vivo* study for the whole NCS; Petitgrain mandarin oil is not expected to be photoallergenic. The local respiratory toxicity endpoint for this NCS was evaluated using the inhalation TTC for a Cramer Class III material, and the inhalation exposure to Petitgrain mandarin oil is below the TTC (0.47 mg/day). Based on the component assessment, Petitgrain mandarin oil does not contain PBT or vPvB components as per the IFRA Environmental Standards and does not present a risk to the aquatic environment at the current reported volumes of use.

3. Component identification

See Table 3 for Component Identification. See Table 4 for Additional Component Information.

Table 2
Additional NCS information.

Exposure[a]		UV/Vis Absorbance (nm)	VoU (Metric Tonnage Per Year)[d]	Cramer Classification[e]
Chronic Systemic Exposure μg/kg/day (2019)[b]	Chronic Inhalation Exposure mg/day (2019)[c]			
5.3	0.010	Peak at 350 nm, returning to baseline by 400 nm	10–100 metric tons per year	III

[a] The reported exposure of the natural complex substance is limited to its use as a fragrance material. Note that the total exposure to the individual component of natural complex substance is included when considering the component's use as a discrete fragrance ingredient in the finished product (added as such and if the material is found in a natural complex substances). If there is an IFRA Standard that exists for the discrete fragrance ingredient it is assumed that the fragrance component does not exceed the limit within the individual finished product.

[b] 95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data. 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, 2017).

[c] 95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015a,b, 2017).

[d] Based on the IFRA Volume of Use Survey (IFRA, 2019).

[e] The NCS is a mixture of multiple components, all belonging to different Cramer Classes, and hence, it is not possible to determine a Cramer Class for the whole NCS. Thus, as a conservative measure, the NCS is categorized as a Cramer Class III material. However, if >95% of the NCS components are identified in the same Cramer Class, then the whole NCS is classified in the same Cramer Class, as long as the remaining 5% derived exposure does not exceed the Cramer Class III limit.

Table 3
NCS component identification.

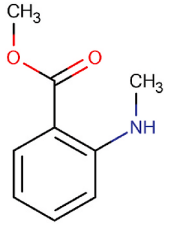
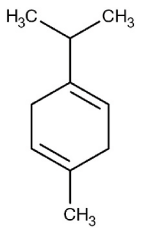
NCS Component Identification		
Material	**Synonyms**	**Structure**
Methyl N-methylanthranilate $C_9H_{11}NO_2$ CAS #: 85-91-6 Log K_{ow}: 2.81 Molecular Weight: 165.19 Vapor Pressure: 0.0131 mm Hg at 20 °C, 0.01 mm Hg at 20 °C, 0.0208 mm Hg at 25 °C Water Solubility: 257 mg/L	Benzoic acid, 2-(methylamino)-, methyl ester Dimethyl anthranilate 2-Methylamino methyl benzoate N-Methylanthranilic acid, methyl ester Methyl o-methylaminobenzoate Methyl 2-methylaminobenzoate N-ｱﾙｷﾙ(C = 1 ~ 4)-o-ｱﾐﾉ安息香酸ｱﾙ ｷﾙ Methyl 2-(methylamino)benzoate	
***p*-Mentha-1,4-diene** $C_{10}H_{16}$ CAS #: 99-85-4 Log K_{ow}: 4.75 Molecular Weight: 136.23 Vapor Pressure: 0.811 mm Hg at 20 °C, 1.15 mm Hg at 25 °C Water Solubility: 3.618 mg/L	Crithmene 1,4-Cyclohexadiene, 1-methyl-4-(1-methylethyl)- 1-Methyl-4-isopropyl-1,4-cyclohexadiene Moslene γ-Terpinene p-ﾒﾝﾀ-1,3-(-3,7 又は-1,4)-ｼﾞｴﾝ 1-Isopropyl-4-methylcyclohexa-1,4-Diene	

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Table 3 (*continued*)

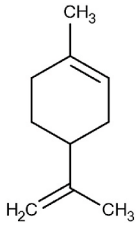
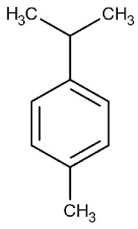
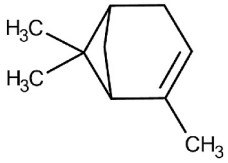
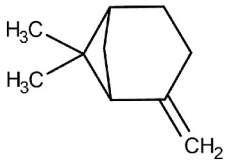
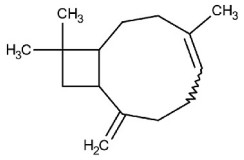
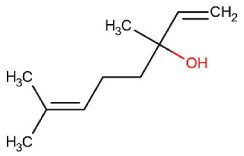
l-Limonene $^{C}10^{H}16$ CAS #: 5989-54-8 Log Kow: 4.83 Molecular Weight: 136.23 Vapor Pressure: 1.03 mm Hg at 20 °C, 1.45 mm Hg at 25 °C Water Solubility: 4.581 mg/L	Cyclohexen, 1-methyl-4-(1-methylethenyl)-, (S)- (S)-p-Mentha-1,8-diene ﾘﾓﾈﾝ 4-Isopropenyl-1-methylcyclohexene	
***p*-Cymene** $^{C}10^{H}14$ CAS #: 99-87-6 Log K_{ow}: 4 Molecular Weight: 134.22 Vapor Pressure: 0.798 mm Hg at 20 °C, 1.14 mm Hg at 25 °C Water Solubility: 27.88 mg/L	Benzene, 1-methyl-4-(1-methylethyl)- Cymene Cymol *p*-Isopropyltoluene *p*-Methylcumene 1-Methyl-4-isopropylbenzene 4-Methyl-1-isopropylbenzene 1-Methyl-4-(1-methylethyl)benzene アルキル（Ｃ＝２～４）トルエン ｼﾒﾝ 1-Isopropyl-4-methylbenzene Cymeme, *para*-p&f drum	
α-Pinene $^{C}10^{H}16$ CAS #: 80-56-8 Log K_{ow}: 4.37 ± 0.24, 5.5 (RIFM, 2022c), 5.7 (RIFM, 2022c), 5.3 (RIFM, 2022c), 5.6 (RIFM, 2022c), 5.7 at 35 °C (RIFM, 2022c), 4.27 Molecular Weight: 136.23 Vapor Pressure: 2.93 mm Hg at 20 °C, 3.2 mm Hg at 20 °C, 4.02 mm Hg at 25 °C Water Solubility: 4.071 mg/L	Bicyclo(3.1.1)hept-2-ene, 2,6,6-trimethyl- Pinene Pin-2(3)-ene 2-Pinene 2,6,6-Trimethylbicyclo-(3,1,1)-2-Heptene ﾋﾟﾈﾝ 2,6,6-Trimethylbicyclo[3.1.1]hept-2-Ene	
β-Pinene $^{C}10^{H}16$ CAS #: 127-91-3 Log K_{ow}: 4.37 ± 0.24, 5.4 at 35 °C (RIFM, 1998), 4.35 Molecular Weight: 136.23 Vapor Pressure: 1.8 mm Hg at 20 °C, 2.2 mm Hg at 20 °C, 2.51 mm Hg at 25 °C Water Solubility: 7.061 mg/L	Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene- 6,6-Dimethyl-2-methylenebicyclo(3.1.1)heptane 6,6-Dimethyl-2-methylenenorpinane Nopinene 2(10)-Pinene Pseudopinene ﾋﾟﾈﾝ 6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptane	
β-Caryophyllene $^{C}15^{H}24$ CAS #: 87-44-5 Log K_{ow}: 6.3, 6.23 ± 0.15 at 25 ± 1 °C (RIFM, 2022d) Molecular Weight: 204.35 Vapor Pressure: 0.02 mm Hg at 20 °C, 0.007 mm Hg at 20 °C, 0.0312 mm Hg at 25 °C Water Solubility: 0.05011 mg/L	Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, [1R-(1R*,4E,9S*)]- Caryophyllene 2-Methylene-6,10,10-trimethylbicyclo(7.2.0.)undecene-5- ene ｶﾘｵﾌｨﾚﾝ 4,11,11-Trimethyl-8-methylenebicyclo[7.2.0]undec-4-Ene Caryophyllene Nat. Rect.	
Linalool $^{C}10^{H}18^{O}$ CAS #: 78-70-6 Log K_{ow}: 3.28 ± 0.26, 2.84 at 25 °C (RIFM, 2022e), 2.9 (RIFM, 2022e), 3.38 Molecular Weight: 154.25 Vapor Pressure: 0.0521 mm Hg at 20 °C, 0.05 mm Hg at 20 °C, 0.0832 mm Hg at 25 °C Water Solubility: 683.7 mg/L	Coriandrol 3,7-Dimethyl-1,6-octadien-3-ol 2,6-Dimethyl-2,7-octadien-6-ol Licareol Linalol 1,6-Octadien-3-ol, 3,7-dimethyl- 2,7-Octadien-6-ol, 2,6-dimethyl- Linalyl alcohol 3,7-ｼﾞﾒﾁﾙ-1,6-ｵｸﾀｼﾞｴﾝ-3-ｵｰﾙ 3,7-Dimethylocta-1,6-dien-3-ol Petinerol Farnesol KS	

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Table 3 (*continued*)

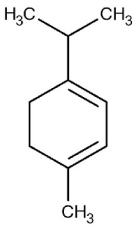
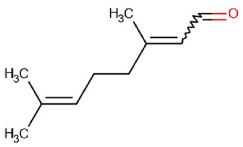
***p*-Mentha-1,3-diene** $^{C}10^{H}16$ CAS #: 99-86-5 Log K_{ow}: 4.75 Molecular Weight: 136.23 Vapor Pressure: 1.18 mm Hg at 20 °C,0.5 mm Hg at 20 °C, 1.66 mm Hg at 25 °C Water Solubility: 5.915 mg/L	1,3-Cyclohexadiene, 1-methyl-4-(1-methylethyl)- 1-Methyl-4-isopropyl-1,3-cyclohexadiene Terpilene α-Terpinene ｐ - メンタ - １，３（ - ３，７又は - １，４） - ジエン 1-Isopropyl-4-methylcyclohexa-1,3- diene Citronella Terpenes	
Citral C10H16O CAS #: 5392-40-5 Log K_{ow}: 3.0 and 3.1 at 35 °C (two isomers) (RIFM, 2006), 3.45 Molecular Weight: 152.23 Vapor Pressure: 0.0596 mm Hg at 20 °C, 0.07 mm Hg at 20 °C, 0.0913 mm Hg at 25 °C Water Solubility: 84.71 mg/L	Citral pure 3,7-Dimethyl-2,6-octadienal Geranial and neral Lemarome Neral and geranial 2,6-Octadienal, 3,7-dimethyl- Citral Lemarome N ｼﾄﾗｰﾙ 3,7-Dimethylocta-2,6-dienal Citral E.Q. Citral Extra Citral refined Citral P Citral N	

Table 4
Additional NCS component information.

Additional Natural Complex Substance Component Information								
CAS #	**Component Principal Name**	**Typical Composition (%)**[a]	**Cramer Class**	Derived exposure[a]		Derived Worldwide VoU Tonnage Bands (metric ton per year)	UV/Vis absorption	
				Systemic μg/kg/day	**Inhalation mg/day**		**UV Spectra Benchmark (1000 L · mol^{-1} · cm^{-1})**	**Read-across Material (if any)**
85-91-6	Methyl N-methylanthranilate	50	II	2.7	0.0050	10–100	above	
99-85-4	*p*-Mentha-1,4-diene	25	I	1.3	0.0025	1–10	below	
5989-54-8	*l*-Limonene	9.9	I	0.52	0.00099	1–10	below	
99-87-6	*p*-Cymene	4.2	I	0.22	0.00042	0.1–1	below	
80-56-8	α-Pinene	2.6	I	0.14	0.00026	0.1–1	below	
127-91-3	β-Pinene	2.4	I	0.13	0.00024	0.1–1	below	
87-44-5	β-Caryophyllene	1.1	I	0.058	0.00011	0.1–1	below	
78-70-6	Linalool	0.83	I	0.044	0.000083	0.1–1	below	
99-86-5	*p*-Mentha-1,3- diene	0.22	I	0.012	0.000022	<0.1	below	
5392-40-5	Citral	0.14	I	0.0074	0.000014	<0.1	below	

[a] Using 2 significant figures.

4. Additional information

Read-across justification: see Section 8 below

Endpoints using read-across analogs: genotoxicity, repeated dose toxicity, reproductive toxicity, skin sensitization.

Disclaimers

The above typical composition of Petitgrain mandarin oil (the "Material") was used by the Expert Panel for Fragrance Safety in this safety assessment for purposes of exposure characterization.

This composition was prepared by the IFRA Natural Complex Substance Task Force following the procedure detailed in IFRA (2021). This Task Force is made of industry experts with knowledge of the predominant materials currently in use and acknowledging the variability inherent in the growth, sourcing, processing, and production of natural materials.

This composition does not and should not be used to represent a standard specification of the Material for use in material production or for regulatory compliance. Its sole purpose is to enable exposure assessment necessary to determine its risk to human health and the environment when used in fragrance applications.

Any endpoint within this safety assessment using component-based evaluation is using exposures that are derived from the whole substance exposure. These derived exposures are based on the percent composition data available for each component within the NCS. Refer to "The RIFM approach to evaluating Natural Complex Substances (NCS)"

(Api et al., 2022).

Any company referencing a RIFM Safety Assessment is responsible for determining if their material is sufficiently chemically similar to this listed Material, and if the assessment applies to their specific material.

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

5. Abbreviation/definition list

2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
CMR - Carcinogenic, Mutagenic, and Reprotoxic
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., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GHS - Globally Harmonized System of Classification and Labelling of Chemicals
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
NCS – Natural Complex Substance
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR -Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

6. Human health summary

6.1. Genotoxicity

Risk assessment

There is insufficient data assessing the mutagenic and clastogenic activity of petitgrain mandarin oil, therefore an analysis of the individual components was performed. Genotoxicity analysis of individual components of petitgrain mandarin oil has been presented in the respective references (see Table 5 below). Exposure to the whole substance is above the TTC for genotoxicity. Components assessed in the BlueScreen assay were found to be negative for genotoxicity. Based on the available target or read-across data, all components were considered negative for mutagenicity and clastogenicity (see Table 5, below) and do not present a concern for genotoxic potential.

Additional References: None.

Table 5
Genotoxicity analysis for the components of the assessed NCS.

NCS Genotoxicity						
CAS #	Component Principal Name	TTC for Genotoxicity	BlueScreen	Mutagenicity	Clastogenicity	References
85-91-6	Methyl N-methylanthranilate	Above	Negative	Negative	Negative	RIFM, 2022a
99-85-4	*p*-Mentha-1,4-diene	Above	Not performed	Negative	Negative	RIFM, 2021b
5989-54-8	*l*-Limonene	Above	Not performed	Negative	Negative	RIFM, 2022b
99-87-6	*p*-Cymene	Above	Not performed	Negative	Negative	RIFM, 2021c
80-56-8	α-Pinene	Above	Negative	Negative	Negative	RIFM, 2022c
127-91-3	β-Pinene	Above	Negative	Negative	Negative	RIFM, 1983; RIFM, 2014
87-44-5	β-Caryophyllene	Above	Not performed	Negative	Negative	RIFM, 2022d
78-70-6	Linalool	Above	Not performed	Negative	Negative	RIFM, 2022e
99-86-5	*p*-Mentha-1,3-diene	Above	Negative	Negative	Negative	RIFM, 2022f
5392-40-5	Citral	Above	Negative	Negative	Negative	RIFM, 2020

Table 6
Repeated dose toxicity analysis for the components of the assessed NCS.

NCS Repeated Dose						
CAS #	Component Principal Name	Read-across CAS # (if any)	Guideline/Duration	NOAEL (mg/kg/day)	MOE[a]	References
85-91-6	Methyl N- methylanthranilate	–	13 weeks (similar to OECD 408)	244	90,370	RIFM, 2022a
99-85-4	*p*-Mentha-1,4-diene	–	OECD 422	250	192,308	RIFM, 2021b
5989-54-8	*l*-Limonene	5989-27-5 (isomer)	NTP, 104 weeks	500	961,538	RIFM, 2022b
99-87-6	*p*-Cymene	–	OECD 422	16.7	75,909	RIFM, 2021c
80-56-8	α-Pinene	–	NTP, 14 weeks	118	842,857	RIFM, 2022c
127-91-3	β-Pinene	79-92-5	OECD 407	83.3	640,769	ECHA REACH Dossier: 79-92-5 (ECHA, 2011a)
87-44-5	β-Caryophyllene	–	OECD 408	1033	17,810,345	RIFM, 2022d
78-70-6	Linalool	–	13 weeks	200	4,545,455	RIFM, 2022e
99-86-5	*p*-Mentha-1,3- diene	4221-98-1	OECD 422	8.33	694,167	RIFM, 2022f
5392-40-5	Citral	–	NTP, 104 weeks	20	2,702,703	RIFM, 2020

[a] In the above table, MOE was calculated using the derived exposure by dividing the NOAEL (mg/kg/day) for each component (or appropriate read-across) by the total systemic exposure
(mg/kg/day) to the respective component as derived in Table 4 above.

Literature Search and Risk Assessment Completed On: 07/02/21.

6.2. Repeated dose toxicity

Risk assessment

The total systemic exposure to petitgrain mandarin oil (5.34 μg/kg/day) is above the TTC (1.5 μg/kg/day; Kroes et al., 2007; see Table 2) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use (see Table 1). Thus, the safety of petitgrain mandarin oil was evaluated based on its constituents and their respective safety data summary (see Tables 3 and 6).

The margin of exposure for each component of petitgrain mandarin oil is adequate for the repeated dose toxicity endpoint at the current level of use. Additionally, the exposure of each component lacking target

Table 7
Developmental Toxicity & Fertility analysis for the components of the assessed NCS.

NCS Reproductive Toxicity											
CAS #	Component Principal Name	Developmental Toxicity					Fertility				
		Read-across CAS # (if any)	Guide- line/ Duration	NOAEL (mg/kg/day)	MOE[a]	References	Read-across CAS # (if any)	Guide-line/ Duration	NOAEL (mg/kg/day)	MOE[a]	References
85-91-6	Methyl N-methylanthranilate	134-20-3	414	768.4	284,593	RIFM, 2012a	134-20-3	422	556	205,926	ECHA REACH Dossier: 134-20-3 (ECHA, 2017b)
99-85-4	*p*-Mentha-1,4-diene	–	422	250	192,308	RIFM, 2021b	–	422	75.29	57,915	RIFM, 2021b
5989-54-8	*l*-Limonene	–	EPA Prenatal developmental toxicity (OPPTS 870.3700)	250	480,769	RIFM, 2022b	–	NTP, 2-year carcinogenicity	2000	3,846,154	RIFM, 2022b
99-87-6	*p*-Cymene	–	422	50	227,273	RIFM, 2021c	–	422	50	227,273	RIFM, 2021c
80-56-8	α-Pinene	–	421	358	2,557,143	RIFM, 2022c	–	NTP (3 months)	118	842,857	RIFM, 2022c
127-91-3	β-Pinene	79-92-5	414	1000	7,692,308	ECHA REACH Dossier: 79-92-5 (ECHA, 2011b)	Exposure is below TTC				–
87-44-5	β-Caryophyllene	Exposure is below TTC				RIFM, 2022d	–	408	1367	23,568,966	RIFM, 2022d
78-70-6	Linalool	–	Prenatal developmental toxicity	1000	22,727,273	RIFM, 2022e	29,171-20-8	421	750	17,045,455	RIFM, 2022e
99-86-5	*p*-Mentha-1,3-diene	–	422	30	2,500,000	RIFM, 2022f	4221-98-1	422	200	16,666,667	RIFM, 2022f
5392-40-5	Citral	–	414	60	8,108,108	RIFM, 2020	–	421	1000	135,135,135	RIFM, 2020

[a] In the above table, MOE was calculated using the derived exposure by dividing the NOAEL (mg/kg/day) for each component by the total systemic exposure (mg/kg/day) to the respective component as derived in Table 4 above.

data or read-across is below TTC. Therefore, with respect to repeated dose toxicity, there are no safety concerns for petitgrain mandarin oil at the current use level.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/16/21.

6.3. Reproductive toxicity

Risk assessment

The total systemic exposure to petitgrain mandarin oil (5.34 μg/kg/day) is above the TTC (1.5 μg/kg/day; Kroes et al., 2007; see Table 2) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use. Thus, the safety of petitgrain mandarin oil was evaluated based on its constituents and their respective safety data summary (see Table 7).

The margin of exposure for each component of the petitgrain mandarin oil is adequate for the reproductive toxicity endpoint at the current level of use. Additionally, the exposure of each component lacking target data or read-across is below TTC. Therefore, with respect to reproductive toxicity, there are no safety concerns for petitgrain mandarin oil at the current use level.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/06/21.

6.4. Skin sensitization

No sensitization data are currently available on petitgrain mandarin oil. Existing data on the components suggest that petitgrain mandarin oil is not a concern for skin sensitization under the current, declared levels of use.

Skin sensitization risk assessment on NCS

No skin sensitization studies are currently available for petitgrain mandarin oil (CAS # 8014-17-3, Material ID 1046095). Acting conservatively with the insufficient available data, the reported exposure of the petitgrain mandarin oil was analyzed and compared to the dermal sensitization threshold (DST) for reactive materials. The current exposure from the 95th percentile concentration is above the DST when evaluated in all QRA categories (RIFM, 2019).

Additional References: None.

Skin sensitization analysis for the components of the assessed NCS

In order to assess the skin sensitization potential of petitgrain mandarin oil, each component of petitgrain mandarin oil was assessed individually. The assessment of each component is summarized in Table 8. If sufficient skin sensitization studies on the target or read-across materials indicate that there is no evidence of sensitization, these components are considered to be safe under the current use levels in the context of this NCS. In cases where existing data or read-across materials indicate that the component is a sensitizer, a defined Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) is provided. For these materials, the current exposure of these sensitizers used in the NCS was derived from multiplying the current 95th percentile concentration of the NCS by the reported typical percentage of the component in the NCS. This derived exposure of each component was benchmarked against 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. (2020). The derived exposures for 2 of the sensitizers are shown as examples, along with their maximum acceptable concentrations in finished products, in Table 9. Citral (CAS # 5392-40-5), a weak sensitizer, is the most potent skin sensitizer among the components, with the lowest NESIL. In addition, the derived exposure for α-pinene (CAS # 80-56-8) is shown in Table 10, along with the maximum acceptable concentrations in finished products. α-Pinene is the most abundant sensitizing component in this NCS. **The derived exposure for all the sensitizers, including the examples shown, is below the maximum acceptable concentrations in finished products.**

When insufficient skin sensitization studies are available and no appropriate read-across analog can be found, the reactivity of the component as well as its metabolites and autoxidation products with skin proteins is assessed by the Expert Panel for Fragrance Safety, utilizing the existing data, information from structural analysis, and *in silico* tools (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Depending on the reactivity of the component and its metabolites and autoxidation products, the derived exposure of the component is benchmarked utilizing the non-reactive DST of 900 μg/cm^2 or reactive DST of 64 μg/cm^2 (Roberts et al., 2015; Safford et al., 2015a,b). The derived exposures represent maximum acceptable concentrations for all DST-applicable components based on the DST approach. **The derived**

Table 8
The Skin Sensitization Data on the Components of Petitgrain mandarin oil. Sufficient skin sensitization studies on the target or read-across materials indicate that there is no risk of sensitization, these components are considered to be safe under the current use levels in the context of this NCS.

NCS Skin Sensitization						
CAS #	Component Principal Name	Typical Composition (%)	Existing Data on the Component[a]	Read- across (if any)	NESIL (μg/cm^2) or DST[b]	References
85-91-6	Methyl N-methylanthranilate	50	Sufficient		NS[C]	RIFM, 2022a
99-85-4	*p*-Mentha-1,4- diene	25	Sufficient		NS[C]	RIFM, 2021b
5989-54-8	*l*-Limonene	9.9	Sufficient		$_{NS}$C,d	RIFM, 2022b
99-87-6	*p*-Cymene	4.2	Insufficient	98-82-8	NS[C]	RIFM, 2021c
80-56-8	α-Pinene	2.6	Sufficient		7000	RIFM, 2022c
127-91-3	β-Pinene	2.4	Sufficient		7000	RIFM, 2021a
87-44-5	β-Caryophyllene	1.1	Sufficient		NS[C]	RIFM, 2022d
78-70-6	Linalool	0.83	Sufficient		NS[C]	RIFM, 2022e
99-86-5	*p*-Mentha-1,3- diene	0.22	Sufficient		2200	RIFM, 2022f
5392-40-5	Citral	0.14	Sufficient		1400	RIFM, 2020

[a] Skin sensitization data on the component and/or its isomers are considered.

[b] Dermal sensitization threshold: When insufficient data are available on the target material or the read-across material, the derived exposure of each component was benchmarked against the reactive DST of 64 μg/cm^{2}or the non-reactive DST of 900 μg/cm^2. To determine the appropriate DST, the chemical structure of each component and its metabolites and autoxidation products were evaluated for its reactivity to skin proteins by the Expert Panel for Fragrance Safety, utilizing Toxtree v3.1.0; OECD Toolbox v4.2. [c]No evidence of sensitization: Sufficient skin sensitization studies are available on the target or read-across materials to conclude that there is no evidence of sensitization.[d]Whereas *d*- and *l*-limonene in the absence of oxidation are not considered to be sensitizing, autoxidation products of these materials would be expected to be contact allergens. *Dl*-Limonene (racemic), and natural products rich in *dl*-limonene (racemic), are subject to an IFRA Standard that defines a Good Manufacturing Practice specification limiting peroxide levels to 20 mmol/L with a recommendation to add an antioxidant at the time of production (IFRA, 2004).

Table 9
The derived exposures in finished products for citral (CAS # 5392-40-5), a weak skin sensitizer itself, but the most potent sensitizer in Petitgrain Mandarin Oil, are all below the Maximum Acceptable Concentrations[a] in the finished products based on a reference dose of 0.6 mg/kg/day, a predicted skin absorption value of 80%, and a NESIL of 1400 μg/cm^2.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] (%) for an Individual Component in Finished Products	Derived Exposure (%) for Citral[c]	Conclusion: Components are considered safe under the current use levels in the context of this NCS
1	Products applied to the lips (lipstick)	0.11	1.0×10^{-5}	Yes
2	Products applied to the axillae	0.032	1.1×10^{-4}	Yes
3	Products applied to the face using fingertips	0.10	1.3×10^{-5}	Yes
4	Products related to fine fragrances	0.60	2.2×10^{-4}	Yes
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.15	1.3×10^{-4}	Yes
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.15	1.4×10^{-5}	Yes
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.15	2.2×10^{-5}	Yes
5D	Baby cream, oil, talc	0.051	No Data[d]	No Data[d]
6	Products with oral and lip exposure	0.35	2.1×10^{-6}	Yes
7	Products applied to the hair with some hand contact	0.20	1.7×10^{-5}	Yes
8	Products with significant ano-genital exposure (tampon)	0.051	No Data[d]	No Data[d]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.2	7.4×10^{-5}	Yes
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.2	3.1×10^{-7}	Yes
10B	Aerosol air freshener	4.2	8.7×10^{-6}	Yes
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.051	No Data[d]	No Data[d]
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.0014	Yes

The reported exposure (and derived exposure) of the NCS is limited to its use as a fragrance material. Note that the total exposure to the individual component of NCS is included when considering the component's use as a discrete fragrance ingredient in the finished product (added as such and if the material is found in an NCS). If there is an IFRA Standard that exists for the discrete fragrance ingredient it is assumed that the fragrance component does not exceed the limit within the individual finished product, irrespective of whether it is added as such or *via* its presence in NCS.

Note: Maximum Acceptable Concentrations in final consumer products shall apply regardless of whether the restricted substance is added directly or indirectly to the fragrance mixture. Indirect contributions from other sources, e.g., presence in natural complex substances (NCS), must be taken into account in the calculation of the levels of the restricted substance.

[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 citral, the basis was the reference dose of 0.6 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1400 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] The derived exposures are calculated by multiplying the percentage of the component in the NCS and the reported 95th percentile use concentrations of the NCS, obtained from the Creme RIFM aggregate exposure model.

[d] Fragrance exposure from these product types are very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Table 10
The derived exposures for α-pinene (CAS # 80-56-8), the most abundant sensitizer in Petitgrain Mandarin Oil, in finished products are all below the Maximum Acceptable Concentrations[a] in the finished products based on a reference dose of 1.18 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7000 μg/cm^2.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] (%) for an Individual Component in Finished Products	Derived Exposure (%) for α-Pinene[c]	Conclusion: Components are considered safe under the current use levels in the context of this NCS
1	Products applied to the lips (lipstick)	0.54	1.9×10^{-4}	Yes
2	Products applied to the axillae	0.16	0.0020	Yes
3	Products applied to the face using fingertips	0.73	2.4×10^{-4}	Yes
4	Products related to fine fragrances	3.0	0.0041	Yes
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.76	0.0024	Yes
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.76	2.7×10^{-4}	Yes
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.76	4.0×10^{-4}	Yes
5D	Baby cream, oil, talc	0.25%	No Data[d]	No Data[d]
6	Products with oral and lip exposure	1.8%	3.9×10^{-5}	Yes
7	Products applied to the hair with some hand contact	1.5	3.1×10^{-4}	Yes
8	Products with significant ano-genital exposure (tampon)	0.25	No Data[d]	No Data[d]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.9	0.0014	Yes
10A	Household care products with mostly hand contact (hand dishwashing detergent)	6.6	5.7×10^{-6}	Yes
10B	Aerosol air freshener	7.3	1.6×10^{-4}	Yes
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.25	No Data[d]	No Data[d]
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.026	Yes

The reported exposure (and derived exposure) of the NCS is limited to its use as a fragrance material. Note that the total exposure to the individual component of NCS is included when considering the component's use as a discrete fragrance ingredient in the finished product (added as such and if the material is found in an NCS). If there is an IFRA Standard that exists for the discrete fragrance ingredient it is assumed that the fragrance component does not exceed the limit within the individual finished product, irrespective of whether it is added as such or *via* its presence in NCS.
Note: Maximum Acceptable Concentrations in final consumer products shall apply regardless of whether the restricted substance is added directly or indirectly to the fragrance mixture. Indirect contributions from other sources, e.g., presence in natural complex substances (NCS), must be taken into account in the calculation of the levels of the restricted substance.

[a] Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For α-pinene, the basis was a reference dose of 1.18 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7000 μg/cm^2.

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

[c] The derived exposures are calculated by multiplying the percentage of the component in the NCS and the reported 95th percentile use concentrations of the NCS, obtained from Creme RIFM aggregate exposure model.

[d] Fragrance exposure from these product types is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

exposures of all DST-applicable components were below the DST when evaluated in all QRA categories. However, additional studies may show they could be used at higher levels.

Literature Search and Risk Assessment Completed On: 05/03/22.

Below are examples of the most potent and most abundant sensitizing components of Petitgrain Mandarin oil, provided to show the safety of this material under the current conditions of use (see Tables 9 and 10).

6.5. Photoirritation/photoallergenicity

Based on UV/Vis absorbance, available *in vitro* study data, and compositional information indicating more than 50% methyl N-methylanthranilate, petitgrain mandarin oil has the potential to cause photoirritation. However, under the current declared levels of use, it is not a concern for photoirritation. Based on existing human data for the component of concern, petitgrain mandarin oil does not present a concern for photoallergy.

Analogs Identified/Justification: None.

Risk assessment

The available UV/Vis absorbance spectrum for petitgrain mandarin oil indicates absorbance peaking at 350 nm and returning to baseline by 400 nm (RIFM, 2010). UV/Vis absorbance spectra for the components of petitgrain mandarin oil, or suitable read-across analogs, indicate that just 1 component, methyl N-methylanthranilate, demonstrates significant absorbance (see Table 4 above and UV Spectra Analysis below). In an *in vitro* 3t3-Neutral Red Uptake photoirritation study, petitgrain mandarin oil was predicted to be photoirritating (RIFM, 2010). Petitgrain mandarin oil typically contains more than 50% methyl N-methylanthranilate. Methyl N-methylanthranilate is a photoirritant with a NOEL of 0.5% and a maximum acceptable concentration of 0.1% (RIFM, 2022a). The derived dermal exposure of the component of concern, methyl N-methylanthranilate, was compared to the maximum acceptable concentration in all QRA categories (see Table 11 below). It did not exceed the maximum acceptable concentration, and, thus, petitgrain mandarin oil is not a concern for photoirritation under the current, declared levels of use. Methyl N- methylanthranilate did not cause photoallergy in human subjects at 0.5% (RIFM, 2022a). While furocoumarins were not reported to be components of petitgrain mandarin

Table 11
The derived exposure for methyl N-methylanthranilate (CAS # 85-91-6) in finished products are all below the maximum acceptable concentrations[a] in the finished products based on a No effect level of 0.5%.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] for an Individual Component in Finished Products Based on No Effect Level of 0.5%	Derived Exposure for methyl N-methylanthranilate[c]
1	Products applied to the lips (lipstick)	0.10%	3.6×10^{-3}%
2	Products applied to the axillae	0.10%	3.5×10^{-2}%
3	Products applied to the face/body using fingertips	0.10%	4.1×10^{-3}%
4	Products related to fine fragrances	0.10%	7.9×10^{-2}%
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.10%	4.6×10^{-2}%
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.10%	5.2×10^{-3}%
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.10%	7.8×10^{-3}%
5D	Baby cream, oil, talc	0.10%	No Data[d]
6	Products with oral and lip exposure	0.10%	7.5×10^{-4}%
7A	Products applied to the hair with some hand contact	0.50%	1.5×10^{-2}%
7B	Products with significant ano-genital exposure (tampon)	0.10%	No Data[d]
8	Products with significant ano-genital exposure (tampon)	0.10%	No Data[d]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.50%	1.5×10^{-2}%
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.50%	1.1×10^{-4}%
10B	Aerosol air freshener	0.10%	3.4×10^{-3}%
11A	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure	No Restriction	No Data[d]
11B	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure	0.10%	No Data[d]
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.0014%

[a] Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For methyl N-methylanthranilate, the basis was a reference dose of 2.44 mg/kg/day, a photoirritation NOEL of 0.5%; (Maximum Acceptable Concentration = 0.1%), and a measured skin absorption value of 29.3%.
[b] For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December, 2019).
[c] The derived exposures are calculated by multiplying the percentage of the component in the NCS and the reported 95th percentile use concentrations of the NCS, obtained from the Creme RIFM aggregate exposure model.
[d] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM aggregate exposure model.

oil, it should be noted that, depending on the processing method, NCSs derived from citrus may contain these potent photoirritants (NTP, 2000). To avoid photoirritant effects, the level of furocoumarins in finished consumer products applied to areas potentially exposed to UV irradiation should not exceed 5 ppm for leave-on products and 50 ppm for rinse-off products (Api et al., 2015). Petitgrain mandarin oil does not present a concern for photoirritation under the current, declared levels of use. Petitgrain mandarin oil does not present a concern for photoallergy.

UV Spectra Analysis

UV/Vis absorption spectra for the whole substance indicate peak absorbance at 350 nm, with a return to baseline by 400 nm (RIFM, 2010). Only 1 of the components of petitgrain mandarin oil, methyl N-methylanthranilate, demonstrated significant UV absorbance. The UV absorption spectrum for methyl N-methylanthranilate demonstrates that this material absorbs in the region of 290–700 nm, with peak absorbance at 350 nm and returning to baseline by 410 nm. The molar absorption coefficient (6120 L $mol^{-1} \cdot cm^{-1}$) for peak absorbance between 290 and 700 nm is above 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: 10/28/21.

6.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for Petitgrain mandarin oil is below the Cramer Class III TTC value for inhalation exposure local effects.

Risk assessment

There are no inhalation data available on Petitgrain mandarin oil. Based on the Creme RIFM Model, the inhalation exposure for NCS is 0.010 mg/day. This exposure is 47 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/21.

7. Environmental summary

7.1. Environmental endpoint summary screening-level assessment

A screening-level risk assessment of petitgrain mandarin oil (based on components assessment) was performed following the RIFM Environmental Framework (Salvito et al., 2002; Safford, 2008), which provides 3 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

Table 12
Persistence and bioaccumulation key data.

NCS Persistence					
CAS #	Component Principal Name	Bioaccumulation (L/kg)	Reference	Persistence	Reference
85-91-6	Methyl N-methylanthranilate	33.3	EPI Suite v4.11; US EPA, 2012a	52.8% (OECD 301D)	ECHA REACH Dossier: 85-91-6 (ECHA, 2016)
99-85-4	*p*-Mentha-1,4- diene	432.6	EPI Suite v4.11; US EPA, 2012a	75% (MITI test)	Ministry of International Trade and Industry, 1988
5989-54-8	*l*-Limonene	360.5	EPI Suite v4.11; US EPA, 2012a	85% (OECD 301D)	ECHA REACH Dossier: 5989-54-8 (ECHA, 2013)
99-87-6	*p*-Cymene	235.6	EPI Suite v4.11; US EPA, 2012a	88% (OECD 301C)	ECHA REACH Dossier: 99-87-6 (ECHA, 2019)
80-56-8	α-Pinene	394.9	EPI Suite v4.11; US EPA, 2012a	68% (OECD 301D)	ECHA REACH Dossier: 80-56-8 (ECHA, 2011b)
127-91-3	β-Pinene	258.1	EPI Suite v4.11; US EPA, 2012a	81% (OECD 301F)	RIFM, 2012b
87-44-5	β-Caryophyllene	6682	EPI Suite v4.11; US EPA, 2012a	70% (OECD 301F)	RIFM, 2007
78-70-6	Linalool	42.33	EPI Suite v4.11; US EPA, 2012a	100% (OECD 302B)	RIFM, 1977
99-86-5	*p*-Mentha-1,3- diene	295.9	EPI Suite v4.11; US EPA, 2012a	66% (OECD 301F)	ECHA REACH Dossier: 99-86-5 (ECHA, 2018)
5392-40-5	Citral	87.14	EPI Suite v4.11; US EPA, 2012a	72% (OECD 301C)	RIFM, 1991

Table 13
Ecotoxicological Key Data and PNEC Derivation for Individual Components (all endpoints reported in mg/L; PNECs in μg/L).

NCS Ecotoxicity				
CAS #	Component Principal Name	Critical Ecotoxicity Endpoint (mg/L)	RIFM PNEC (μg/L)	Reference
85-91-6	Methyl N-methylanthranilate	96-h algae EC50: 5.28	0.0528	EPI Suite v4.11; US EPA, 2012a
99-85-4	*p*-Mentha-1,4- diene	48-h *Daphnia magna* LC50: 0.278	0.0278	EPI Suite v4.11; US EPA, 2012a
5989-54-8	*l*-Limonene	48-h *Daphnia magna* LC50: 0.238	0.0238	EPI Suite v4.11; US EPA, 2012a
99-87-6	*p*-Cymene	48-h *Daphnia magna* LC50: 1.213	0.1213	EPI Suite v4.11; US EPA, 2012a
80-56-8	α-Pinene	48-h *Daphnia magna* LC50: 0.719	0.0719	EPI Suite v4.11; US EPA, 2012a
127-91-3	β-Pinene	48-h *Daphnia magna* LC50: 0.615	0.0615	EPI Suite v4.11; US EPA, 2012a
87-44-5	β-Caryophyllene	48-h *Daphnia magna* LC50: 0.019	0.0019	EPI Suite v4.11; US EPA, 2012a
78-70-6	Linalool	Fish LC50: 34.23	0.03423	Salvito et al., 2002
99-86-5	*p*-Mentha-1,3- diene	Fish LC50: 0.8213	0.0008213	Salvito et al., 2002
5392-40-5	Citral	Fish LC50: 22.63	0.02263	Salvito et al., 2002

Table 14
Exposure information and PEC calculation (following the RIFM environmental framework: Salvito et al., 2002; Safford et al., 2011).

NCS Environmental Exposure						
CAS #	Component Principal Name	KOW	Biodegradation Factor	Dilution Factor	Regional VoU Tonnage Band	Risk Characterization PEC/PNEC
85-91-6	Methyl N-methylanthranilate	2.8	0.1	3	1–10	<1
99-85′-4	*p*-Mentha-1,4- diene	4.7	1	3	1–10	<1
5989-54-8	*l*-Limonene	4.8	1	3	1–10	<1
99-87-6	*p*-Cymene	4	1	3	<1	<1
80-56-8	α-Pinene	5.3	1	3	<1	<1
127-91-3	β-Pinene	5.4	1	3	<1	<1
87-44-5	β-Caryophyllene	6.2	1	3	<1	<1
78-70-6	Linalool	2.9	0	3	<1	<1
99-86-5	*p*-Mentha-1,3- diene	4.7	0	3	<1	<1
5392-40-5	Citral	3.1	0	3	<1	<1

Based on the individual component analysis, the RQ for this material is < 1. No further assessment is necessary.

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 tables below (see Tables 12–14). For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC for each component is then calculated using its percentage in the NCS and the actual regional tonnage for the whole NCS. Following the RIFM Environmental Framework and based on components assessment, petitgrain mandarin oil 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) did not identify petitgrain mandarin oil as possibly persistent or bioaccumulative based on individual components structures and

Table 15
Read-across justification.

NCS Read-across Summary Table		
Target Component	Read-across Analog (Endpoint)	Reference
85-91-6 Methyl N-methylanthranilate	Methyl anthranilate, CAS # 134-20-3 (developmental toxicity); formaldehyde, CAS # 50-00-0 (developmental toxicity)	RIFM, 2022a
99-85-4 *p*-Mentha-1,4- diene	No read-across used for this material	N/A
5989-54-8 *L*-Limonene	*d*-Limonene, CAS # 5989-27-5 (repeated dose toxicity and skin sensitization)	RIFM, 2022b
99-87-6 *p*-Cymene	Cumene, CAS # 98-82-8 (skin sensitization)	RIFM, 2021c
80-56-8 α-Pinene	No read-across used for this material	N/A
127-91-3 β-Pinene	Camphene, CAS # 79-92-5 (repeated dose and developmental toxicity)	See justification below
87-44-5 β-Caryophyllene	No read-across used for this material	N/A
78-70-6 Linalool	Dehydrolinalool, CAS # 29,171-20-8 (fertility)	RIFM, 2022e
99-86-5 *p*-Mentha-1,3- diene	(−)-(R)-α-Phellandrene, CAS # 4221-98-1 (repeated dose toxicity, fertility)	RIFM, 2022f
5392-40-5 Citral	No read-across used for this material	N/A

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, 2017a). 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-awaystudies), 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 summarized below.

Literature Search and Risk Assessment Completed On: 03/24/22.

8. READ-ACROSS Justification

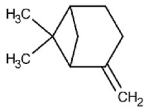
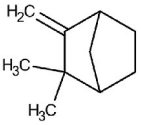
8.1. Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). 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, 2017c).

- 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, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010). Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system (See Table 15 below for the Read-across Justification.).

Target material β-pinene (CAS 127-91-3) read-across justification summary

There are insufficient toxicity data on β-pinene (CAS # 127-91-3). 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, camphene (CAS # 79-92-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

	Target Material	Read-across Material
Principal Name	β-Pinene	Camphene
CAS No.	127-91-3	79-92-5
Structure		
Similarity (Tanimoto Score)		0.89
Endpoint		Repeated dose toxicity Developmental toxicity
Molecular Formula	$^{C}10^{H}16$	$^{C}10^{H}16$
Molecular Weight (g/mol)	136.24	136.24
Melting Point (°C, EPI Suite)	−61.00	52.00
Boiling Point (°C, EPI Suite)	166.00	159.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	390.63	333.31
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISuite)	7.06	4.60
Log K_{OW}	4.16	4.22
J_{max} (μg/cm2/h, **SAM)**	1.38	0.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6879.97	16313.33
Repeated Dose Toxicity		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Repeated Dose (HESS)	Aliphatic/Alicyclic hydrocarbons (Alpha 2u-globulin nephropathy) Rank C	Aliphatic/Alicyclic hydrocarbons (Alpha 2u-globulin nephropathy) Rank C
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)	Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Conclusions

Camphene (CAS # 79-92-5) was used as a read-across analog for the target material, β-pinene (CAS # 127-91-3), for the developmental toxicity and repeated dose toxicity endpoints.

The target substance and the read-across analog belong to the class of bicyclic monoterpenes.

The target substance and the read-across analog share a 2,2- dimethylbicyclo-heptene substructure.

The key difference between the target substance and the read-across analog is that the target has [3.3.1] bicyclic rings while the read-across has [2.2.1] bicyclic rings. The target substance and the read-across analog are structural isomers. This structural difference is toxicologically insignificant.

Similarity between the target substance 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 substance 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 substance and the read-across analog.

The target substance and the read-across analog have HESS alerts of aliphatic/alicyclic hydrocarbons (α-2u-globulin nephropathy) Rank C for repeated dose toxicity. The pathological accumulation of hyaline droplets in the proximal renal tubules of male rats is considered to be a consequence of α-2u-globulin binding to administrated chemicals or their metabolites (α-2u-globulin nephropathy). This toxicity does not occur in humans. For the α-2u-globulin nephropathy induced by aliphatic/alicyclic hydrocarbons, it was reported that a calculated n-octanol-water partition coefficient above 3.5 and the presence of an isopentyl structural moiety within a particular range of molecular size appear to be associated with hyaline droplet accumulation-inducing activity in aliphatics. Most of these criteria do not match with the structures of the target substance or the read-across analog. The data described in the reproductive toxicity and repeated dose toxicity sections

Confirm that the margin of exposure is adequate under the current usage. Therefore, the alert is superseded by the data.

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.

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 related to this article can be found at https://doi.org/10.1016/j.fct.2022.113575.

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