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Short Review

RIFM natural complex substance (NCS) fragrance ingredient safety assessment, Mandarin oil terpenes, CAS registry number 68953-04-8, RIFM ID 250-G2.30

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ARTICLE INFO

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1. Natural complex substance (NCS) identification

Mandarin oil terpenes, CAS # 68953-04-8, RIFM ID 250-G2.30. 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.

Mandarin oil terpenes was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photo-irritation/photoallergenicity, skin sensitization, and environmental safety. Data for the components of the NCS do not show a concern for

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Table 1
NCS Identification.

NCS	Synonyms
NCS Name: Mandarin oil terpenes **CAS #** 68953-04-8 **Material ID:** 1043338 **RIFM ID:** 250-G2.30 **Percent Composition Known:** 100% **Family:** Rutaceae **Genus:** *Citrus* **Botanical Definition:** Fruit **Processing Method:** Terpenes	Terpenes and terpenoids, mandarin-oil *Citrus reticulata* Blanco Mandarin orange extract Rutaceae *Citrus reticulata Citrus nobilis* Lour.

genotoxicity. Mandarin oil terpenes 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 Threshold of Toxicological Concern (TTC); mandarin oil terpenes is safe for use under the conditions described in this safety assessment for the repeated dose and reproductive toxicity endpoints. Data for the 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 ultraviolet/visible (UV/Vis) absorption spectra for the components or read-across components of the NCS; mandarin oil terpenes is not expected to be photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis absorption spectra for the components or read-across components of the NCS; mandarin oil terpenes 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 mandarin oil terpenes is below the TTC (0.47 mg/day). Based on the component assessment, mandarin oil terpenes does not contain Persistent, Bioaccumulative, and Toxic (PBT) or (very) Persistent, (very) Bioaccumulative (vPvB) components as per the International Fragrance Association (IFRA) Environmental Standards and does not present a risk to the aquatic environment at the current reported volumes of use (VoU).

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 (2021)[b]	Chronic Inhalation Exposure mg/day (2021)[c]			
4.4	0.0029	Not Available	1–10 metric tons per year	I

[a] The reported 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.

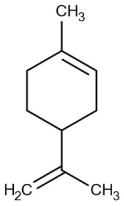
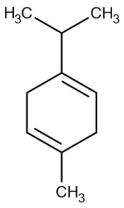
[b] 95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, D. et al., 2015 Safford, B. et al., 2015 Safford, B. et al., 2017 Comiskey, D. et al., 2017).

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

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

[e] NCS are a mixture of multiple components that may belong to different Cramer Classes, and hence, it would not be possible to determine a Cramer Class for the whole NCS. Typically, as a conservative measure, the NCS would be categorized as a Cramer Class III material. However, in this case, >95% of the NCS components are identified in the same Cramer Class (Class I), and so the whole NCS is classified in the same Cramer Class as well, since the remaining 5% derived exposure does not exceed the Cramer Class III limit.

Table 3
NCS component Identification.

NCS Component Identification		
Material	Synonyms	Structure
***d*-Limonene** C10H16 CAS #: 5989-27-5 Log Kow: 5.3 at 45 °C (RIFM, 2022a), 4.83 Molecular Weight: 136.23 g/mol Vapor Pressure: 1.03 mm Hg at 20 °C, 1.2 mm Hg at 20 °C, 1.45 mm Hg at 25 °C Water Solubility: 4.581 mg/L	Cyclohexene, 1-methyl-4-(1-methylethenyl)-, (R)-*p*-1,8(9)-Menthadiene *d*-*p*-Mentha-1,8-diene (R)-(+)-*p*-Mentha-1,8-diene *d*-1-Methyl-4-isopropenyl-1-cyclohexene Limonene Limonene Extra ﾘﾓﾈﾝ 4-Isopropenyl-1-methylcyclohexene (R)-*p*-Mentha-1,8-diene	
***p*-Mentha-1,4-diene** C10H16 CAS #: 99-85-4 Log Kow: 4.75 Molecular Weight: 136.23 g/mol 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	

(*continued on next page*)

Table 3 (*continued*)

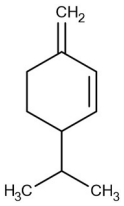
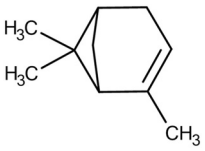
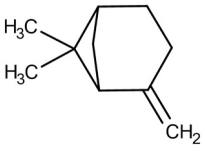
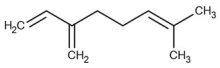
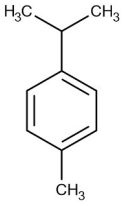
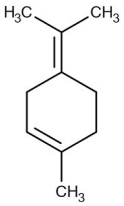
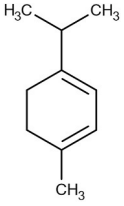
NCS Component Identification		
Material	Synonyms	Structure
β-Phellandrene C10H16 CAS #: 555-10-2 Log Kow: 4.7 Molecular Weight: 136.23 g/mol Vapor Pressure: 1.95 mm Hg at 25 °C Water Solubility: 2.452 mg/L	6-Isopropyl-3-methylene-cyclohexene *p*-Mentha-1(7),2-diene 3-Isopropyl-6-methylenecyclohexene Cyclohexene, 3-methylene-6-(1-methylethyl)-	
α-Pinene C10H16 CAS #: 80-56-8 Log Kow: 4.37 ± 0.24, 5.5 (RIFM, 2022b), 5.7 (RIFM, 2022b), 5.3 (RIFM, 2022b), 5.6 (RIFM, 2022b), 5.7 at 35 °C (RIFM, 2022b), 4.27 Molecular Weight: 136.23 g/mol 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	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 Bicyclo(3.1.1)hept-2-ene, 2,6,6-trimethyl-	
β-Pinene C10H16 CAS #: 127-91-3 Log Kow: 4.37 ± 0.24, 5.4 at 35 °C (RIFM, 1998), 4.35 Molecular Weight: 136.23 g/mol 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	
Myrcene C10H16 CAS #: 123-35-3 Log Kow: 5.1 at 35 °C (RIFM, 2020), 4.88 Molecular Weight: 136.23 g/mol Vapor Pressure: 1.72 mm Hg at 20 °C, 1.5 mm Hg at 20 °C, 2.4 mm Hg at 25 °C Water Solubility: 6.923 mg/L	7-Methyl-3-methylene-1,6-octadiene β-Myrcene 1,6-Octadiene, 7-methyl-3-methylene- Myrcene 90 ７ - メチル - ３ - メチレン - １，６ - オクタジエン 7-Methyl-3-methyleneocta-1,6-diene	
***p*-Cymene** C10H14 CAS #: 99-87-6 Log Kow: 4 Molecular Weight: 134.22 g/mol 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	
Terpinolene C10H16 CAS #: 586-62-9 Log Kow: 3.3, 3.5, 5.3; 5.3 at 30 °C (RIFM, 2022c), 4.88 Molecular Weight: 136.23 g/mol Vapor Pressure: 0.702 mm Hg at 20 °C, 0.5 mm Hg at 20 °C, 1 mm Hg at 25 °C Water Solubility: 3.838 mg/L	Cyclohexene, 1-methyl-4-(1-methylethylidene)-*p*-Mentha-1,4(8)-diene 1-Methyl-4-isopropylidene-1-cyclohexene 1,4(8)-Terpadiene Terpinene 1,4-ﾃﾚﾋﾟﾉﾚﾝ 4-Isopropylidene-1-methylcyclohexene	
***p*-Mentha-1,3-diene** C10H16 CAS #: 99-86-5 Log Kow: 4.75 Molecular Weight: 136.23 g/mol 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	

Table 4
Additional NCS component information.

Additional Natural Complex Substance Component Information								
CAS #	Component Principal Name	Typical Composition (%) *	Cramer Class	Derived Exposure		Derived Worldwide VoU Tonnage Bands (Metric Tons 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 Applicable)
5989-27-5	*d*-Limonene	75	I	3.3	0.0022	1–10	below	
99-85-4	*p*-Mentha-1,4-diene	14	I	0.62	0.00041	<1	below	
555-10-2	β-Phellandrene	3.1	I	0.14	0.000090	<1	below	
80-56-8	α-Pinene	2.1	I	0.092	0.000061	<1	below	
127-91-3	β-Pinene	1.9	I	0.084	0.000055	<1	below	
123-35-3	Myrcene	1.7	I	0.075	0.000049	<1	below	
99-87-6	*p*-Cymene	0.97	I	0.043	0.000028	<1	below	
586-62-9	Terpinolene	0.56	I	0.025	0.000016	<1	below	
99-86-5	*p*-Mentha-1,3-diene	0.17	I	0.0075	0.0000049	<1	below	

4. Additional information

Read-across justification: See Section 9 below.

Endpoints using read-across analogs: Repeated dose toxicity, skin sensitization.

Disclaimers

The above typical composition of mandarin oil terpenes (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.

5. Conclusion

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

6. Abbreviation/definition list

2-Box Model A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF Assessment Factor
BCF Bioconcentration Factor
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; Safford et al., 2015a; Safford et al., 2017; Comiskey 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

7. Human health summary

7.1. Genotoxicity

7.1.1. Risk assessment

There is insufficient data assessing the mutagenic and clastogenic activity of mandarin oil terpenes (material ID 1043338), therefore an analysis of the individual components was performed. Genotoxicity analysis of individual components of mandarin oil terpenes (material ID 1043338) is presented in the respective references (see table below). Exposure to the whole substance is above TTC for genotoxicity. Components assessed in the Bluescreen assay were found to be negative for genotoxicity. Based on the target or read-across data available, all components were considered negative for mutagenicity and clastogenicity (see Table 5) and do not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/23.

7.2. Repeated dose toxicity risk assessment

The total systemic exposure to mandarin oil terpenes (4.4 μg/kg bw/day) is above the TTC (30 μg/kg bw/day; Kroes, 2007; see Table 2) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use. Thus, the safety of mandarin oil terpenes was evaluated based on its constituents and their respective safety data summary (see Table 6).

The margin of exposure (MOE) for each component of the mandarin oil terpenes is adequate for the repeated dose 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 repeated dose toxicity, there are no safety concerns for mandarin oil terpenes at the current use level.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/07/23.

7.3. Reproductive toxicity risk assessment

The total systemic exposure to mandarin oil terpenes (4.4 μg/kg bw/day) is above the TTC (30 μg/kg bw/day; Kroes, 2007; see Table 2) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use. Thus, the safety of mandarin oil terpenes was evaluated based on its constituents and their respective safety data summary (Table 7).

The MOE for each component of the mandarin oil terpenes 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 mandarin oil terpenes at the current use level.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/07/23.

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

NCS Genotoxicity						
CAS #	Component Principal Name	TTC for Genotoxicity	BlueScreen	Mutagenicity	Clastogenicity	References
5989-27-5	*d*-Limonene	Above	Not performed	Negative	Negative	RIFM (2022a)
99-85-4	*p*-Mentha-1,4- diene	Above	Not performed	Negative	Negative	RIFM, 2021b
555-10-2	β-Phellandrene	Above	Not performed	Negative	Negative	RIFM, 2022e; RIFM, 2022f
80-56-8	α-Pinene	Above	Negative	Negative	Negative	RIFM (2022b)
127-91-3	β-Pinene	Above	Negative	Negative	Negative	RIFM, 1983; RIFM, 2014
123-35-3	Myrcene	Above	Not performed	Negative	Negative	RIFM, 2020
99-87-6	*p*-Cymene	Above	Not performed	Negative	Negative	RIFM, 2021c
586-62-9	Terpinolene	Above	Not performed	Negative	Negative	RIFM, 2022c
99-86-5	*p*-Mentha-1,3- diene	Above	Negative	Negative	Negative	RIFM (2022d)

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
5989-27-5	*d*-Limonene	–	NTP, 104 weeks	500	151717	RIFM (2022a)
99-85-4	*p*-Mentha-1,4- diene	–	OECD 422	83.3	140236	RIFM, 2021b
555-10-2	β-Phellandrene	Exposure is below TTC				–
80-56-8	α-Pinene	–	NTP, 14 weeks	118	1271004	RIFM (2022b)
127-91-3	β-Pinene	18172-67-3 (isomer)	OECD 422	203	2454062	RIFM (2019)
123-35-3	Myrcene	–	NTP, 104 weeks	25	326541	RIFM, 2020
99-87-6	*p*-Cymene	–	OECD 422	16.7	391284	RIFM, 2021c
586-62-9	Terpinolene	–	OECD 422	52	2110390	RIFM, 2022c
99-86-5	*p*-Mentha-1,3- diene	4221-98-1	OECD 422	8.33	1113636	RIFM (2022d)

[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.

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**	References	Read-across CAS # (if any)	Guide-line/ Duration	NOAEL (mg/kg/ day)	MOE**	References
5989-27-5	*d*-Limonene	–	EPA developmental toxicity Study	250	75858	RIFM (2022a)	–	NTP, 13-week study	2000	606869	RIFM (2022a)
99-85-4	*p*-Mentha- 1,4-diene	–	422	250	420875	RIFM, 2021b	–	422	75.29	126751	RIFM, 2021b
555-10-2	β-Phellandrene	–	TTC			–	–	TTC			–
80-56-8	α-Pinene	–	421	358	3856097	RIFM (2022b)	–	NTP 14-week study	118	1271004	RIFM (2022b)
127-91-3	β-Pinene	–	422	608	7350097	RIFM (2019)	–	422	608	7350097	RIFM (2019)
123-35-3	Myrcene	–	414, 415	250	3265413	RIFM, 2020	–	415	300	3918495	RIFM, 2020
99-87-6	*p*-Cymene	–	422	50	1171509	RIFM, 2021c	–	422	50	1171509	RIFM, 2021c
586-62-9	Terpinolene	–	422	155	6290584	RIFM, 2022c	–	422	295	11972403	RIFM, 2022c
99-86-5	*p*-Mentha- 1,3-diene	–	422	30	4010695	RIFM (2022d)	–	422	200	26737968	RIFM (2022d)

7.4. Skin sensitization

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

7.4.1. Skin sensitization risk assessment on NCS

No skin sensitization studies are currently available for mandarin oil terpenes (CAS # 68953-04-8, Material ID 1043338). Acting conservatively with the insufficient available data, the reported exposure of mandarin oil terpenes 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, 2021a).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/17/23.

7.4.2. Skin sensitization analysis for the components of the assessed NCS

In order to assess the skin sensitization potential of mandarin oil terpenes, each component 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

Table 8
The Skin Sensitization Data on the Components of Mandarin oil terpenes. 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
5989-27-5	*d*-Limonene	75	Sufficient		NS[c,d]	RIFM (2022a)
99-85-4	*p*-Mentha-1,4- diene	14	Sufficient		NS[c]	RIFM, 2021b
555-10-2	β-Phellandrene	3.1	Insufficient		Reactive DST	–
80-56-8	α-Pinene	2.1	Sufficient		7000	RIFM (2022b)
127-91-3	β-Pinene	1.9	Sufficient		7200	RIFM (2021d)
123-35-3	Myrcene	1.7	Sufficient		NSc	RIFM, 2020
99-87-6	*p*-Cymene	0.97	Insufficient	99-82-8	NSc	RIFM, 2021c
586-62-9	Terpinolene	0.56	Insufficient	5989-54-8	NSc	RIFM, 2022c
99-86-5	*p*-Mentha-1,3- diene	0.17	Sufficient		2200	RIFM (2022d)

[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 v4.5.

[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, 1995).

component is a sensitizer, a defined Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) is provided (see Table 8). 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. (Api, 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, *p*-mentha-1,3-diene (CAS # 99-86-5), a moderate 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), a weak sensitizer, is shown in Table 10, along with the maximum acceptable finished products. α-Pinene is the most abundant sensitizing component in this NCS. **The derived exposure for all 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 can be found, the reactivity of the component as well as its metabolites and autoxidation products to the skin proteins is assessed by the Expert Panel for Fragrance Safety, utilizing the information from structural analysis and *in silico* tools (Roberts, 2007b; Toxtree v3.1.0; OECD Toolbox v4.5). 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 (Safford, R.J., 2008; Safford, R.J. et al., 2011; Roberts, D.W. et al., 2015; Safford, R.J. et al., 2015). The derived exposures of all these materials are below the DST when evaluated in all QRA categories. The derived exposures represent

Table 9
The derived exposure in finished products for *p*-mentha-1,3-diene (CAS # 99-86-5), a moderate skin sensitizer itself, but the most potent sensitizer in mandarin oil terpenes, are all below the Maximum Acceptable Concentrations[a] in the finished products based on a reference dose of 0.083 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2200 μg/cm^2 (RIFM, 2022d).

IFRACategory[b]	Description of Product Type	Maximum Acceptable Concentrations[a] (%) for an Individual Component in Finished Products Based on NESIL of 2200 μg/cm^2	Derived Exposure (%) for p-mentha-1,3- diene[c]	Conclusion: Components are considered safe under the current use levels in the context of this NCS
1	Products applied to the lips (lipstick)	0.059	3.4×10^{-6}	Yes
2	Products applied to the axillae	0.050	1.6×10^{-4}	Yes
3	Products applied to the face using fingertips	0.024	6.8×10^{-5}	Yes
4	Products related to fine fragrances	0.53	0.0013	Yes
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave- on	0.11	1.5×10^{-4}	Yes
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.024	2.65×10^{-5}	Yes
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave- on	0.024	2.4×10^{-5}	Yes
5D	Baby cream, oil, talc	0.0078	No Data[d]	No Data[d]
6	Products with oral and lip exposure	0.18	0.0061	Yes
7	Products applied to the hair with some hand contact	0.012	5.8×10^{-5}	Yes
8	Products with significant ano- genital exposure (tampon)	0.078	No Data[d]	No Data[d]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.094	2.5×10^{-4}	Yes
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.49	0.0012	Yes
10B	Aerosol air freshener	0.13	1.1×10^{-4}	Yes
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0078	No Data[d]	No Data[d]
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	5.3	0.0037	Yes

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 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 *p*-mentha-1,3-diene, the basis was the reference dose of 0.083 mg/kg/day, a p redicted skin absorption value of 40%, and a skin sensitization NESIL of 2200 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 95 percentile use concentrations of the NCS, obtained from the Creme RIFM Aggregate Exposure Model. 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 a 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.

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

Table 10
The derived exposure for α-pinene (CAS # 80-56-8), a weak sensitizer, the most abundant sensitizer in mandarin oil terpenes, 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 (RIFM, 2022b).

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] (%) for an Individual Component in Finished Products Based on NESIL of 7000 μg/cm^2	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	2.8×10^{-7}	Yes
2	Products applied to the axillae	0.16	1.3×10^{-5}	Yes
3	Products applied to the face using fingertips	0.73	5.5×10^{-6}	Yes
4	Products related to fine fragrances	3.0	1.0×10^{-4}	Yes
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.76	1.2×10^{-5}	Yes
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.76	2.0×10^{-6}	Yes
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.76	2.0×10^{-6}	Yes
5D	Baby cream, oil, talc	0.25	No Data[d]	No Data[d]
6	Products with oral and lip exposure	1.8	4.9×10^{-4}	Yes
7	Products applied to the hair with some hand contact	1.5	4.7×10^{-6}	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	2.1×10^{-5}	Yes
10A	Household care products with mostly hand contact (hand dishwashing detergent)	6.6	9.9×10^{-5}	Yes
10B	Aerosol air freshener	7.3	9.0×10^{-6}	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	3.0×10^{-4}	Yes

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 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 the 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 ().

[c] The derived exposures are calculated by multiplying the percentage of the component in the NCS and the reported 95 percentile use concentrations of the NCS, obtained from the Creme RIFM Aggregate Exposure Model. 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 an 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.

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

maximum acceptable concentrations for all DST-applicable components based on the DST approach. The derived 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/17/23.

Below are examples of the most potent and most abundant sensitizing components of Mandarin oil terpenes, provided to show the safety of this material under the current conditions of use.

7.5. Photoirritation/photoallergenicity

Based on the available UV/Vis spectra for the components or read-across analogs, mandarin oil terpenes would not be expected to present a concern for photoirritation or photoallergenicity.

Analogs Identified/Justification: None.

7.5.1. Risk assessment

There are no photosafety studies available for mandarin oil terpenes in experimental models. UV/Vis absorption spectra for mandarin oil terpenes are not available. UV/Vis absorption spectra for each component, or a read-across analog, indicate no absorption between 290 and 700 nm (see Table 4). Corresponding molar absorption coefficients are below the benchmark of concern for photoirritation and photoallergenicity (Henry, B. et al., 2009). Depending on the processing method, NCS derived from citrus may contain furucoumarins, potent photoirritants (NTP, 2000). To avoid photoirritant effects, the levels of furocoumarins in finished consumer products that may be applied to sun-exposed areas should not exceed 5 ppm for leave-on products and 50 ppm for rinse-off products. Based on the lack of absorbance for all of the components of the whole material, mandarin oil terpenes does not present a concern for photoirritation or photoallergenicity.

7.5.2. UV spectra analysis

UV/Vis absorption spectra for mandarin oil terpenes not available. UV/Vis absorption spectra for each component, or a read-across analog, were available and indicated no significant absorbance between 290 and

700 nm (see Table 4). Molar absorption coefficients for each component or read-across analog were below the benchmark of concern for photoirritation and photoallergenicity, 1000 L $mol^{-1} \cdot cm^{-1}$ (see Table 4) (Henry, B. et al., 2009).

Literature Search and Risk Assessment Completed On: 02/24/23.

7.6. Local respiratory toxicity

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

Risk assessment

There are no inhalation data available on mandarin oil terpenes. Based on the Creme RIFM Model, the inhalation exposure for NCS is 0.0029 mg/day. This exposure is 482.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/19/23.

8. Environmental summary

8.1. Environmental endpoint summary screening-level assessment

A screening-level risk assessment of mandarin oil terpenes (based on components assessment) was performed following the RIFM Environmental Framework (Salvito, 2002) which provides for 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 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 for each component is then calculated using its percentage in the oil and the actual regional tonnage for the whole oil. Following the RIFM Environmental Framework and based on individual components assessment mandarin oil terpenes 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 mandarin oil terpenes as possibly persistent or bioaccumulative based on individual components structures and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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 = 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 summarized below (see Tables 11–14).

Table 11
Persistence and bioaccumulation Key data.

NCS Persistence					
CAS #	Component Principal Name	Bioaccumulation (L/Kg)	Reference	Persistence	Reference
5989-27-5	*d*-Limonene	360	EPI Suite v4.11; US EPA, 2012a	71.4% (OECD 301B)	RIFM (2022a)
99-85-4	*p*-Mentha- 1,4-diene	432	EPI Suite v4.11; US EPA, 2012a	27% (OECD 301F)	RIFM, 2021b
555-10-2	β- Phellandrene	584	EPI Suite v4.11; US EPA, 2012a	2.89	EPI Suite v4.11; US EPA, 2012a
80-56-8	α-Pinene	394	EPI Suite v4.11; US EPA, 2012a	68% (OECD 301D)	RIFM (2022b)
127-91-3	β-Pinene	258	EPI Suite v4.11; US EPA, 2012a	81%(OECD 301F)	RIFM, 2012
123-35-3	Myrcene	262	EPI Suite v4.11; US EPA, 2012a	76% (OECD 301D)	RIFM, 2020
99-87-6	*p*-Cymene	235	EPI Suite v4.11; US EPA, 2012a	88% (OECD 301C)	RIFM, 2021c
586-62-9	Terpinolene	413	EPI Suite v4.11; US EPA, 2012a	80% (OECD 302C)	RIFM, 2022c
99-86-5	*p*-Mentha- 1,3-diene	295.9	EPI Suite v4.11; US EPA, 2012a	66%(OECD 301F)	RIFM (2022d)

Table 12
Ecotoxicological Key Data and PNEC Derivation for Individual Components (all endpoints reported in mg/L; PNECs in μg/L).

NCS Ecotox				
CAS #	Component Principal Name	Critical Ecotoxicity Endpoint (mg/L)	RIFM PNEC (μg/L)	Reference
5989-27-5	*d*-Limonene	48-h *Daphnia magna* LC50: 0.238	0.0238	ECOSAR v2.0; US EPA, 2012b
99-85-4	*p*-Mentha-1,4-diene	48-h *Daphnia magna* LC50: 0.278	0.0278	ECOSAR v2.0; US EPA, 2012b
555-10-2	β-Phellandrene	Fish LC50: 0.8213	0.0008213	Salvito et al., 2002
80-56-8	α-Pinene	48-h *Daphnia magna* LC50: 0.719	0.0719	ECOSAR v2.0; US EPA, 2012b
127-91-3	β-Pinene	Fish LC50: 0.2021	0.0002021	Salvito et al., 2002
123-35-3	Myrcene	Fish LC50: 3685	0.0003685	Salvito et al., 2002
99-87-6	*p*-Cymene	Fish LC50: 3.289	0.003289	Salvito et al., 2002
586-62-9	Terpinolene	Fish LC50: 0.2469	0.0002469	Salvito et al., 2002
99-86-5	*p*-Mentha-1,3-diene	Fish LC50: 1.232	0.001232	Salvito et al., 2002

Table 13
Exposure information and PEC calculation (following the RIFM environmental framework: Salvito et al., 2002).

NCS Environmental Exposure						
CAS #	Component Principal Name	KOW	Biodegradation Factor	Dilution Factor	Regional Volume of Use Tonnage Band	Risk Characterization PEC/PNEC
5989-27-5	*d*-Limonene	5.3	1	3	1–10	<1
99-85-4	*p*-Mentha-1,4-diene	4.7	1	3	<1	<1
555-10-2	β-Phellandrene	4.7	0	3	<1	<1
80-56-8	α-Pinene	5.7	1	3	<1	<1
127-91-3	β-Pinene	5.4	0	3	<1	<1
123-35-3	Myrcene	5.1	0	3	<1	<1
99-87-6	*p*-Cymene	4.8	0	3	<1	<1
586-62-9	Terpinolene	5.3	0	3	<1	<1
99-86-5	*p*-Mentha-1,3-diene	4.7	0	3	<1	<1

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

Table 14
Read-across justification.

NCS Read-across			
Target Component	Read-across analog	Endpoint	Reference
5989-27-5 *d*-Limonene	N/A	N/A	N/A
99-85-4 *p*-Mentha-1,4-diene	N/A	N/A	N/A
555-10-2 β-Phellandrene	N/A	N/A	N/A
80-56-8 α-Pinene	N/A	N/A	N/A
127-91-3 β-Pinene	N/A	N/A	N/A
123-35-3 Myrcene	N/A	N/A	N/A
99-87-6 *p*-Cymene	99-82-8	Skin sensitization	RIFM, 2021c
586-62-9 Terpinolene	5989-54-8	Skin sensitization	RIFM, 2022c
99-86-5 *p*-Mentha-1,3-diene	4221-98-1	Repeated dose toxicity	RIFM (2022e)

Literature Search and Risk Assessment Completed On: 04/23/23.

9. Read-across justification

9.1. 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, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2–4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2–4.5 (OECD, 2021), 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 v4.2–4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2–4.5 was selected as the choice of the alert system.

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.

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