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Short Review

RIFM Natural Complex Substance (NCS) fragrance ingredient safety assessment, clove bud absolute, CAS Registry Number 8000-34-8, RIFM ID 583-F2.1

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ABSTRACT

Clove bud absolute 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. Clove bud absolute 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); clove bud absolute 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 ultraviolet/visible (UV/Vis) absorption spectra for the components of the NCS; clove bud absolute is not expected to be photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis absorption spectra for the components of the NCS; clove bud absolute 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 clove bud absolute is below the TTC (0.47 mg/day). Based on the component assessment, clove bud absolute does not contain Persistent, Bioaccumulative, and

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Toxic (PBT) or (very) Persistent, (very) Bioaccumulative (vPvB) components as per the IFRA Environmental Standards and does not present a risk to the aquatic environment at the current reported VoU.

1. Natural Complex Substance (NCS) identification

Clove bud absolute, CAS # 8000-34-8, RIFM ID 583-F2.1. See Table 1 for Substance Identification and Table 2 for Additional Information.

2. Summary

There are insufficient toxicity data on 3,7,10-humulatriene (CAS # 6753-98-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, (−)-germacrene D (CAS # 23986-74-5) and myrcene (CAS # 123-35-3) were identified as read-across analogs and α-farnesene (CAS # 502-61-4) was identified as a WoE material with sufficient data for toxicological evaluation.

3. Component identification

See Table 3 for Component Identification (RIFM, 2025). See Table 4 for Additional Component Information.

4. 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; Safford et al., 2015; Safford et al., 2024; 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted.

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.

Table 1
NCS identification.

NCS	Synonyms
NCS Name: Clove bud absolute **CAS #** 8000-34-8 **Material ID:** 1048330 **RIFM ID:** 583-F2.1 **Percent Composition Known:** 91.89 % **Family:** Myrtaceae **Genus:** *Syzygium* **Botanical Definition:** Flower **Processing Method:** Absolute	*Syzygium aromaticum* L.; *Eugenia* spp.; Myrtaceae; *Eugenia caryophyllata*; *Eugenia caryophyllus aromaticus*

Table 2
Additional NCS information.

Exposure[a]		UV/Vis Absorbance (nm)	Volume of Use (VoU) (Metric Tonnage Per Year)[d]	Cramer Classification[e]
Chronic Systemic Exposure μg/kg/day (RIFM, 2023)[b]	Chronic Inhalation Exposure mg/day (RIFM, 2023)[c]			
1.7	0.0034	Not available	0.1–1	III

[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 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 NCS). If an IFRA Standard exists for the discrete fragrance ingredient, the fragrance component is assumed to 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; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; Comiskey et al., 2017).

[c] 95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; Comiskey et al., 2017).

[d] Based on the IFRA VoU 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 composition consists of components with 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.

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.

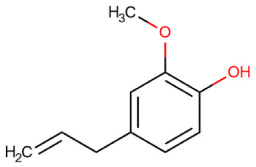
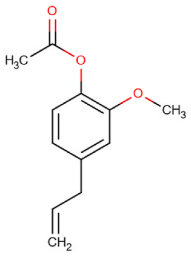
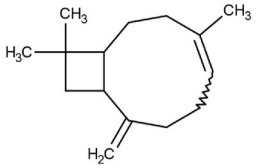
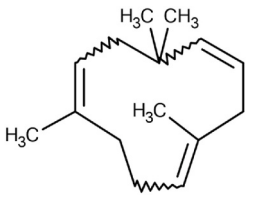
6. Human health summary

6.1. Genotoxicity

6.1.1. Risk Assessment

There are insufficient data assessing the mutagenic and clastogenic activity of clove bud absolute; therefore, an analysis of the individual components was performed. The genotoxicity analysis of individual components of clove bud absolute is presented in the respective references (see Table 5). 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 (Table 5) and do not present a concern for genotoxic potential.

Table 3
NCS component identification.

NCS Component Identification		
Material	Synonyms	2D Structure
Eugenol C10H12O2 CAS #: 97-53-0 Stereochemistry: Log K_{ow} (experimental): 1.83, 2.0, 2.2, 2.4, 2.99; 2.0 at 24 °C Log K_{ow} (calculated): 2.73 Molecular Weight: 164.2 g/mol Vapor Pressure (experimental): 0.03 mm Hg at 25 °C Vapor Pressure (calculated): 0.009 mm Hg at 20 °C, 0.00948 mm Hg Water Solubility (experimental): 2118 mg/L at 20 ± 1 °C Water Solubility (calculated): 1154 mg/L of sol. at 20 ± 0.5 °C, 754 mg/L at 25 °C	4-Allylcatechol-2-methyl ether 4-Allylguaiacol 4-Allyl-2-methoxyphenol 1-Hydroxy-2-methoxy-4-propenylbenzene 4-Hydroxy-3-methoxy-1-allylbenzene 2-Methoxy-4-allylphenol Phenol, 2-methoxy-4-(2-propenyl)-1-Allyl-4-hydroxy-3-methoxybenzene Eugenic acid Caryophyllic acid Allylguaiacol 2-Methoxy-4-(2-propenyl)phenol 1-Hydroxy-2-methoxy-4-allylbenzene 2-Hydroxy-5-allylanisole *o*-ﾒﾄｷｼ-*p*-ｱﾘﾙﾍﾞﾝｾﾞﾝﾌｪﾉｰﾙ Eugenol pure cosmos	
Eugenyl acetate C12H14O3 CAS #: 93-28-7 Stereochemistry: Log K_{ow} (experimental): 2.3, 2.8 Log K_{ow} (calculated): 3.06 Molecular Weight: 206.24 g/mol Vapor Pressure (experimental): 0.041, 0.090, and 3.0 Pa at 20, 25, and 50 °C, respectively Vapor Pressure (calculated): 0.006 mm Hg at 20 °C, 0.00475 mm Hg Water Solubility (experimental): 407 ± 7 mg/L at 20 °C, pH 5.1, 386 mg/L at 20 °C Water Solubility (calculated): 98.28 mg/L at 25 °C	Acetyl eugenol 4-Allyl-2-methoxyphenyl acetate Eugenol acetate 2-Methoxy-4-(2-propen-1-yl)phenyl acetate Phenol, 2-methoxy-4-(2-propenyl)-, acetate アルカン酸(C = 1–2)オイゲニル Phenol, 4-allyl-2-methoxy-, acetate (2-Methoxy-4-prop-2-enylphenyl) acetate 2-Methoxy-4-(2-propenyl)phenol acetate 2-Methoxy-4-(prop-2-en-1-yl)phenyl acetate Aceteugenol Acetyleugenol O-Acetyleugenol	
β-Caryophyllene C15H24 CAS #: 87-44-5 Stereochemistry: Log K_{ow} (experimental): 6.23 ± 0.15 at 25 ± 1 °C Log K_{ow} (calculated): 6.3 Molecular Weight: 204.35 g/mol Vapor Pressure (experimental): <0.1 mbar (20.0 °C), 0.06, 0.09, and 0.45 hPa at 20, 25, and 50 °C, respectively Vapor Pressure (calculated): 0.007 mm Hg at 20 °C, 0.0312 mm Hg Water Solubility (experimental): 0.088 mg/L at 20 °C Water Solubility (calculated): 0.05011 mg/L at 25 °C	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. (−)-*trans*-β-Caryophyllene	
3,7,10-Humulatriene C15H24 CAS #: 6753-98-6 Stereochemistry: Log K_{ow} (experimental): n/a Log K_{ow} (calculated): 6.95 Molecular Weight: 204.35 g/mol Vapor Pressure (experimental): n/a Vapor Pressure (calculated): 0.0153 mm Hg Water Solubility (experimental): n/a Water Solubility (calculated): 0.01396 mg/L at 25 °C	α-Caryophyllene 1,4,8-Cycloundecatriene, 2,6,6,9- tetramethyl-, (E,E,E)-Humulene 2,6,6,9-Tetramethyl-1,4,8- cycloundecatriene 2,6,6,9-Tetramethylcycloundeca-1,4,8- triene α-Humulene	

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/01/24.

6.2. Repeated Dose Toxicity

6.2.1. Risk Assessment

The total systemic exposure to clove bud absolute (1.7 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. Thus, the safety of clove bud absolute was evaluated based on its constituents and their respective safety data summary (Table 6).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/28/24.

6.3. Reproductive Toxicity

6.3.1. Risk Assessment

The total systemic exposure to clove bud absolute (1.7 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 clove bud absolute was evaluated based on its constituents and their respective safety data summary (Table 7).

Additional References**:** None.

Literature Search and Risk Assessment Completed On: 02/28/24.

6.4. Skin Sensitization

No skin sensitization data are available on clove bud absolute. Therefore, the NCS was analyzed on a component basis. Existing data on the components of clove bud absolute suggest that clove bud absolute is not a concern for skin sensitization under the current declared levels of use.

6.4.1. Skin Sensitization Risk Assessment on NCS

No skin sensitization studies are currently available for clove bud absolute. Acting conservatively with the insufficient available data, the reported exposure of clove bud absolute 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, 2023).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/29/24.

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

In order to assess the skin sensitization potential of clove bud absolute, 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 component is a sensitizer, a defined Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) is provided (Table 8). For these materials, the current exposure of these sensitizers used in the NCS was derived by 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 exposure for the one sensitizer component is shown as an example, along with the maximum acceptable concentrations in finished products. The derived exposure for eugenol (CAS # 97-53-0) is shown in Table 9, along with the maximum acceptable concentrations in finished products. Eugenol, a weak sensitizer, is the most potent and 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 (Table 8), 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, D.W. et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Depending on the reactivity, the derived exposure of the component and its metabolites and autoxidation products 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 maximum acceptable concentrations for all DST-applicable components were calculated. 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: 02/29/24.

Below is the most potent and most abundant sensitizing component of clove bud absolute provided to show the safety of this material under the current conditions of use.

Table 4
Additional NCS component information.

Additional NCS 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)
97-53-0	Eugenol	69	I	1.2	0.0023	<1	below	
93-28-7	Eugenyl acetate	13	I	0.22	0.00044	<1	below	
87-44-5	β-Caryophyllene	8.6	I	0.15	0.00029	<1	below	
6753-98-6	3,7,10-Humulatriene	1.1	I	0.019	0.000037	<1	below	

[a] Using 2 significant figures.

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

NCS Genotoxicity						
CAS #	Component Principal Name	TTC for Genotoxicity	BlueScreen	Mutagenicity	Clastogenicity	References
97-53-0	Eugenol	Above	Not performed	Negative	Negative	RIFM (2022b)
93-28-7	Eugenyl acetate	Above	Negative	Negative	Negative from read-across material CAS # 93-29-8	RIFM, 2020a; RIFM, 2017b
87-44-5	β-Caryophyllene	Above	Not performed	Negative	Negative	RIFM (2022a)
6753-98-6	3,7,10-Humulatriene	Above	Not performed	Negative from read-across material CAS # 23986-74-5 and WoE material CAS # 502-61-4	Negative from read-across material CAS # 23986-74-5 and WoE material CAS # 502-61-4	RIFM, 2016; RIFM, 2017a

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
97-53-0	Eugenol		NTP, 14-week	300	255754	RIFM (2022b)
93-28-7	Eugenyl acetate		19-week chronic dietary toxicity study	500	2262443	RIFM (2020a)
87-44-5	β- Caryophyllene		OECD 408	1033	7065663	RIFM (2022a)
6753-98-6	3,7,10-Humulatriene	Exposure is below TTC				

[a] In the above table, the 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)	Guideline/ Duration	NOAEL (mg/kg/ day)	MOE[a]	References	Read-across CAS # (if any)	Guideline/ Duration	NOAEL (mg/kg/ day)	MOE[a]	References
97-53-0	Eugenol		Exposure is below TTC					Exposure is below TTC			
93-28-7	Eugenyl acetate		Exposure is below TTC					Exposure is below TTC			
87-44-5	β- Caryophyllene		Exposure is below TTC					OECD 408	1367	9350205	RIFM (2022a)
6753-98-6	3,7,10-Humulatriene		Exposure is below TTC					Exposure is below TTC			

[a] In the above table, the 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.

Table 8
The skin sensitization data on the components of clove bud absolute. 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
97-53-0	Eugenol	69	Sufficient		5900	RIFM (2022b)
93-28-7	Eugenyl acetate	13	Sufficient		Non-sensitizer (NS)[c]	RIFM (2020a)
87-44-5	β- Caryophyllene	8.6	Sufficient		NS[c]	RIFM (2022a)
6753-98-6	3,7,10-Humulatriene	1.1	Insufficient	123-35-3	NS[c]	RIFM (2020b)

[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 v4.2–4.5.
[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.

6.5. Photoirritation/Photoallergenicity

Based on the UV/Vis absorbance spectra of the components, clove bud absolute would not be expected to present a concern for photoirritation or photoallergenicity.

Analogs Identified/Justification: None.

Table 9
The derived exposure in finished products for eugenol (CAS # 97-53-0), a weak skin sensitizer itself, but the most potent and most abundant sensitizer in clove bud absolute, are all below the Maximum Acceptable Concentrations[b] in the finished products based on a reference dose of 3.0 mg/kg/day, a skin absorption value of 22.6 %, and a skin sensitization NESIL of 5900 μg/cm^2.

IFRACategory[a]	Description of Product Type	Maximum Acceptable Concentrations[b] (%) for an Individual Component in Finished Products Based on NESIL of 5900 μg/cm^2	Derived Exposure (%) for clove bud absolute[c]	Conclusion: Components are considered safe under the current use levels in the context of this NCS
1	Products applied to the lips (lipstick)	0.45	NRU	Yes
2	Products applied to the axillae	0.14	0.0021	Yes
3	Products applied to the face using fingertips	1.0	7.0×10^{-5}	Yes
4	Products related to fine fragrances	2.5	0.061	Yes
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.64	NRU	Yes
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.64	0.0017	Yes
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.64	NRU	Yes
5D	Baby cream, oil, talc	0.21	No Data[d]	No Data[d]
6	Products with oral and lip exposure	1.5	0.021	Yes
7	Products applied to the hair with some hand contact	2.0	6.0×10^{-6}	Yes
8	Products with significant anogenital exposure (tampon)	0.21	No Data[d]	No Data[d]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.9	5.5×10^{-4}	Yes
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.0	NRU	Yes
10B	Aerosol air freshener	18	4.8×10^{-4}	Yes
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.21	No Data[d]	No Data[d]
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.046	Yes

[a] 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).

[b] 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 eugenol, the basis was the reference dose of 3.0 mg/kg/day, a skin absorption value of 22.6 %, and a skin sensitization NESIL of 5900 μg/cm^2. 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.

[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. 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.

6.5.1. Risk Assessment

There are no photosafety studies available for clove bud absolute in experimental models. UV/Vis absorption spectra for clove bud absolute are not available. UV/Vis absorbance spectra were available for all components of clove bud absolute. The available spectra indicate no significant absorbance with corresponding molar absorbance coefficients below the benchmark of concern for photoirritation and photoallergenicity (Henry, B. et al., 2009). Based on the lack of absorbance of the components, clove bud absolute does not present a concern for photoirritation or photoallergenicity.

6.5.2. UV Spectra Analysis

UV/Vis absorption spectra were not available for clove bud absolute. UV/Vis absorbance spectra were available for all the components of clove bud absolute. The available spectra indicate no significant absorbance with corresponding molar absorbance coefficients below the benchmark of concern for photoirritation and photoallergenicity (Henry, B. et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/24.

6.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for clove bud absolute is below the Cramer Class III TTC value for inhalation exposure local effects.

6.6.1. Risk Assessment

There are no inhalation data available on clove bud absolute. Based on the Creme RIFM Model, the inhalation exposure for NCS is 0.0034 mg/day. This exposure is 138.2 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: 02/26/24.

7. Environmental summary

7.1. Environmental Endpoint Summary Screening-level Assessment

A screening-level risk assessment of clove bud absolute (based on component assessment) was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's 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 Tables 10 and 11. For the PEC, the range from the most recent IFRA VoU 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 component assessment, clove bud absolute 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 clove bud absolute as possibly persistent or bioaccumulative based on individual component 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 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 = 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 in Table 12.

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

Literature Search and Risk Assessment Completed On: 02/22/24.

Table 10
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
97-53-0	Eugenol	Fish LC50: 330.2	0.3302	Salvito et al. (2002)
93-28-7	Eugenyl acetate	Fish LC50: 152.3	0.1523	Salvito et al. (2002)
87-44-5	β-Caryophyllene	48-h *Daphnia magna* LC50: 0.019	0.0019	US EPA (2012b)
6753-98-6	3,7,10-Humulatriene	48-h *Daphnia magna* LC50: 0.005	0.0005	US EPA (2012b)

8. READ-ACROSS JUSTIFICATION

8.1. Methods

The read-across analogs (see Table 13) 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 Chemicals 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).

Table 11
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 VoU Tonnage Band	Risk Characterization PEC/PNEC
97-53-0	Eugenol	1.8	0	3	<1	<1
93-28-7	Eugenyl acetate	2.3	0	3	<1	<1
87-44-5	β-Caryophyllene	6.3	1	3	<1	<1
6753-98-6	3,7,10-Humulatriene	6.9	1	3	<1	<1

Table 12
Persistence and bioaccumulation key data.

NCS Persistence					
CAS #	Component Principal Name	Bioaccumulation (L/kg)	Reference	Persistence	Reference
97-53-0	Eugenol	14.61	EPI Suite v4.11; US EPA, 2012a	100.4 % (OECD 301B)	RIFM (1994)
93-28-7	Eugenyl acetate	48.81	EPI Suite v4.11; US EPA, 2012a	81 % (OECD 301F)	RIFM (2011)
87-44-5	β- Caryophyllene	6682	EPI Suite v4.11; US EPA, 2012a	70 % (OECD 301F)	RIFM (2007)
6753-98-6	3,7,10-Humulatriene	17940	EPI Suite v4.11; US EPA, 2012a	71 % (OECD 301F)	RIFM (2009)

- 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.

9. Conclusions

- (−)-Germacrene D (CAS # 23986-74-5) was used as a read-across analog, and α-farnesene (CAS # 502-61-4) was used as a WoE material for the target material 3,7,10-humulatriene (CAS # 6753-98-6) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the unsaturated cyclic hydrocarbon group.
  - The key difference between the target material and the read-across analog is the target material has 3 isolated vinylene groups while the read-across has one isolated vinylene group and a vinyl group and vinylene group in conjugation. α-Farnesene (CAS # 502-61-4) is used as WoE material to show the lack of genotoxic potential from the bis-allylic carbon. The read-across analog and the WoE material contain the structural features of the target material that are relevant to this endpoint and are expected to have equal or greater potential for toxicity as compared to the target material.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Neither the target material nor the read-across analog have alerts for genotoxicity. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Myrcene (CAS # 123-35-3) was used as a read-across analog for the target material 3,7,10- humulatriene (CAS # 6753-98-6) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to the unsaturated hydrocarbon group.
  - The key difference between the target material and the read-across analog is that the target material is a macrocyclic ring with 3 isolated vinylene groups, whereas the read-across analog is a branched chain with 1 isolated vinylene and 2 conjugated vinyl groups. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Neither the target material nor the read-across analog has alerts for skin sensitization. The data on the read-across analog confirms that the material is not a skin sensitizer. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

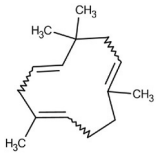
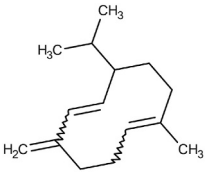
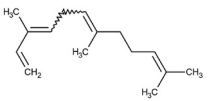
Additional information

Read-across justification: See Section 9 **below**.

Table 13
Read-across justification.

NCS Read-across Summary Table

Target Component	Read-across Analog (Mutagenicity)	Read-across Analog (Clastogenicity)	Read-across Analog (Repeated dose)	Read-across Analog (Developmental)	Read-across Analog (Fertility)	Read-across Analog (Skin sensitization)	Read-across Analog (Photoirritation/ Photoallergy)	Read-across Analog (Local respiratory)	Read-across Analog (Environmental)	Reference
97-53-0 Eugenol										
93-28-7 Eugenyl acetate		93-29-8								RIFM (2020a)
87-44-5 β-Caryophyllene										
6753-98-6 3,7,10-Humulatriene	23986-74-5 and WoE 502-61-4	23986-74-5 and WoE 502-61-4				123-35-3				See below

	Target Material	Read-across Material	WoE Material	Read-across Material
Principal Name	3,7,10-Humulatriene	(−)-Germacrene D	α-Farnesene	Myrcene
CAS No.	6753-98-6	23986-74-5	502-61-4	123-35-3
Structure				
Similarity (Tanimoto Score)		0.58	0.64	0.53
SMILES	CC1CCC═C(C)CC═CC(C) (C)CC = 1	CC(C)C1CCC(C)═CCCC(=C) C═C1	CC(C)═CCCC(C) = CCC═C(C) C═C	CC(C)═CCCC(=C)C═C
Endpoint		Genotoxicity	Genotoxicity	Skin sensitization
Molecular Formula	$C_{15}H_{24}$	$C_{15}H_{24}$	$C_{15}H_{24}$	$C_{10}H_{16}$
Molecular Weight	204.357	204.357	204.357	136.238
Melting Point (°C, EPI Suite)	35.48	15.76	−17.22	−64.83
Boiling Point (°C, EPI Suite)	270.56	262.90	261.11	167.00
Vapor Pressure (Pa at 25 °C, EPI Suite)	2.04E+00	3.04E+00	3.33E+00	2.79E+02
Water Solubility (mg/L, at 25 °C, WSKOW v1.42 in EPI Suite)	1.40E-02	1.28E-02	1.05E-02	4.00E+00
Log KOW	6.95	6.99	7.1	4.33
J_{max} (μg/cm^2/h, SAM)	0.00	0.00	0.00	0.81
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.65E+05	1.13E+05	2.67E+05	9.28E+03
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	Not classified	
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found			No alert found
Protein Binding (OECD)	No alert found			No alert found

(*continued on next page*)

Table 13 (*continued*)

	Target Material	Read-across Material	WoE Material	Read-across Material
Protein Binding Potency	Not possible to classify according to these rules (GSH)			Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found			No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified			No skin sensitization reactivity domain alerts were identified
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Endpoints using read-across analogs: genotoxicity, skin sensitization.

Disclaimers

The above typical composition of clove bud absolute (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.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2025.115415.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118 (104805).

Api, A.M., Belsito, D., Botelho, D., Bruze, M., et al., 2022. The RIFM approach to evaluating natural Complex substances (NCS). Food Chem. Toxicol. 159 (Suppl. 1), 112715.

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

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

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

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

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices

data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718.
ECHA, 2017a. Guidance on information requirements and chemical safety assessment: chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.
ECHA, 2017b. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2019. Volume of Use Survey. January-December 2019.
IFRA (International Fragrance Association), 2021. IFRA Natural Complex Substances (NCS) TF procedure to derive compositional data for NCS. Retrieved from. https://ifrafragrance.org/safe-use/scientific-guidance.
Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352.
OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA 7, 2015. http://www.oecd.org/.
OECD, 2021. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994. The Ultimate Biodegradability of Eugenol in the Sealed Vessel Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International Ltd. RIFM report number 34944.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Ready Biodegradability of Beta-Caryophyllene. Unpublished Report from Givaudan. RIFM Report Number 55348. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Ready Biodegradability of 3,7,10-humulatriene (Alpha-humulene). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 57364.
RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Ready Biodegradability of Eugenyl Acetate. Unpublished Report from Givaudan. RIFM Report Number 62781. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Alpha-Farnesene (Farnesene, Mixture of Isomers): Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69865.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017a. Alpha-Farnesene: in Vitro Human Lymphocyte Micronucleus Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 72856.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. Eugenyl Acetate: Reverse Mutation Assay 'Ames Test' Using Salmonella typhimurium and Escherichia coli. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from PT Indesso Aroma. RIFM report number 76295.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. RIFM fragrance ingredient safety assessment, eugenyl acetate, CAS Registry Number 93-28-7. Food Chem. Toxicol. 144 (111630). Retrieved from. https://fragrancematerialsafetyresource.elsevier.com/sites/default/files/93-28-7.pdf.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. RIFM fragrance ingredient safety assessment, myrcene, CAS Registry Number 123-35-3. Food Chem. Toxicol. 144 (111631). Retrieved from. https://fragrancematerialsafetyresource.elsevier.com/sites/default/files/123-35-3_0.pdf.
RIFM (Research Institute for Fragrance Materials, Inc.), 2022a. RIFM fragrance ingredient safety assessment, β-caryophyllene, CAS Registry Number 87-44-5. Food Chem. Toxicol. 159 (112707). Retrieved from. https://fragrancematerialsafetyresource.elsevier.com/sites/default/files/87-44-5.pdf.
RIFM (Research Institute for Fragrance Materials, Inc.), 2022b. Update to RIFM fragrance ingredient safety assessment, eugenol, CAS Registry Number 97-53-0. Food Chem. Toxicol. 163 (113027). Retrieved from. https://fragrancematerialsafetyresource.elsevier.com/sites/default/files/97-53-0_0.pdf.
RIFM (Research Institute for Fragrance Materials, Inc.), 2023. NCS Exposure Survey 41. August 2023.
RIFM (Research Institute for Fragrance Materials, Inc.), 2025. RIFM fragrance and flavor database. Retrieved from. https://rifmdatabase.rifm.org/rifmweb/home/home-page.
Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products". Regul. Toxicol. Pharmacol. 72 (3), 105545, 673-68]. Regul Toxicol Pharmacol.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.