

# Safety Evaluation of Natural Complex Substances for the Skin Sensitization Endpoint

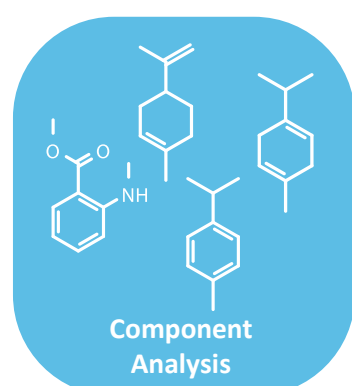
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## Introduction

Natural Complex Substances (NCS) are often used in fragrance formulations as well as cosmetics and other personal care products. NCS are often misconceived as being inherently safe but determining the safety of NCS is actually a challenge facing many industries. The Research Institute for Fragrance Materials, Inc. (RIFM) has evaluated the safety data for fragrance materials for over 53 years. RIFM leverages the knowledge compiled over the years concerning the components of NCS to conduct safety assessment on the NCS. Herein, we describe the tiered approach in the safety evaluation of the NCS for the skin sensitization endpoint. This approach can be outlined into 4 steps; Step 1) evaluation using available data on NCS, 2) benchmarking exposure level of the NCS against the dermal sensitization threshold (DST) 3) component-based evaluation, 4) data generation on NCS. In step 3, the skin sensitization data on the components of the NCS are combined with the exposure data for the quantitative risk assessment of the NCS. Using this approach on a case study, petitgrain mandarin oil was evaluated to be safe under the current use level. This process provides a systematic and comprehensive risk assessment of NCS.

## Evaluation Strategy



### For each component

- Is it a potential skin sensitizer?  
 Safety assessments on individual fragrance ingredients are available  
 → <http://fragrancematerialsafetyresource.elsevier.com/>
- What is the safe use level?  
 RIFM conducts updated approach for quantitative risk assessment (QRA2) to determine how much of the fragrance material can be used in various products safely. (Api et al., 2020)
- Derived exposure for each component < safe use levels based on QRA2 → safe under the current conditions of use

### Reference

Api AM, Basketter D, Bridges J, et al. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul Toxicol Pharmacol. Dec 2020;118:104805.

## Safety Assessment of Petitgrain Mandarin Oil



- No historical skin sensitization data on petitgrain mandarin oil
- The current exposure from the 95th percentile concentration from Creme-RIFM aggregate exposure model is **above the DST** when evaluated in all QRA categories (RIFM, 2019).
- Assessment of all components suggest that **petitgrain mandarin oil is safe for skin sensitization under the current, declared levels of use.**

CAS #	Principal Name	Typical Composition (%)	Existing Data on the component	Read-across (if applicable)	NESIL (µg/cm <sup>2</sup> ) or DST	Reference
85-91-6	Methyl N-methylantranilate	50.1	Sufficient		NS	SA 85-91-6
99-85-4	p-Mentha-1,4-diene	24.6	Sufficient		NS	SA 99-85-4
5989-54-8	l-Limonene	9.9	Sufficient		NS	SA 5989-54-8
99-87-6	p-Cymene	4.6	Insufficient	99-82-8	NS	SA 99-87-6
80-56-8	alpha-Pinene	2.6	Sufficient		7000	SA 80-56-8
127-91-3	β-Pinene	2.4	Insufficient		7000	SA 127-91-3
87-44-5	beta-Caryophyllene	1.1	Sufficient		NS	SA 87-44-5
2867-05-2	alpha-Thujene	0.91	Insufficient	127-91-3	7000	SA 127-91-3
78-70-6	Linalool	0.83	Sufficient		NS	SA 78-70-6
123-35-3	Myrcene	0.67	Sufficient		NS	SA 123-35-3
586-62-9	Terpinolene	0.67	Insufficient	5989-54-8	NS	SA 586-62-9
3387-41-5	Sabinene	0.4	Insufficient		Non reactive DST	SA 3387-41-5
7786-61-0	2-Methoxy 4-vinyl phenol	0.3	Insufficient		Reactive DST	SA 7786-61-0
562-74-3	4-Carvomenthenol	0.22	Sufficient		NS	SA 562-74-3
99-86-5	p-Mentha-1,3-diene	0.22	Sufficient		2200	SA 99-86-5
98-55-5	α-Terpineol	0.15	Sufficient		NS	SA 98-55-5
5392-40-5	Citral	0.14	Sufficient		1400	SA 5392-40-5
134-20-3	Methyl anthranilate	0.12	Insufficient		Reactive DST	None
89-83-8	Thymol	0.11	Insufficient		Reactive DST	None
1195-32-0	para, α-Dimethylstyrene	0.1	Insufficient		Reactive DST	SA 1195-32-0
6753-98-6	3,7,10-Humulatriene	0.1	Insufficient	123-35-3	NS	SA 6753-98-6
1076-56-8	1-Methyl-3-methoxy-4-isopropylbenzene	0.1	Insufficient		Reactive DST	None

Obtained from International Fragrance Association and International Organization of the Flavor Industry's Complex Ingredient Constituent Compendium (IFRA-IOFI CICC)

Questions? Contact Mihwa Na  
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 And check out the full criteria document  
 in Food and Chemical Toxicology →

