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Fragrance material review on farnesol

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ABSTRACT

A toxicologic and dermatologic review of farnesol when used as a fragrance ingredient is presented.

Introduction

In 2006, a complete literature search was conducted on farnesol. Online databases that were surveyed included Chemical Abstract Services and the National Library of Medicine. In addition, fragrance companies were asked to submit pertinent test data. All relevant references are included in this document. More details have been provided for unpublished data. Any papers in which the vehicles and/or the doses are not given have not been included in this review. The number of animals, sex and strain are always provided unless they are not given in the original report or paper.

This individual Fragrance Material Review is not intended as a stand alone document. Please refer to the Toxicologic and Dermatologic Assessment of Cyclic and Non-Cyclic Terpene Alcohols (Belsito et al., 2008) for an overall assessment of this material.

1. Identification (Fig. 1)

1.1 Synonyms: 2,6,10-dodecatrien-1-ol, 3,7,11-trimethyl-; farnesyl alcohol; trimethyl dodecatrienol; 3,7,11-trimethyl-2,6,10-dodecatrien-1-ol.
1.2 CAS registry number: 4602-84-0.
1.3 EINECS number: 225-004-1.
1.4 Formula: $C_{15}H_{26}O$.
1.5 Molecular weight: 222.37.
1.6 Council of Europe: farnesol was included by the Council of Europe in the list of substances granted B – information required – 28-day oral study (COE No. 78).
1.7 Food and Drug Administration: Farnesol was approved by the FDA as GRAS (21 CFR 172.515).
1.8 Flavor and Extract Manufacturers' Association states (FEMA): generally recognized as safe as a flavor ingredient – GRAS. (2478).
1.9 The Joint FAO/WHO Expert Committee on Food Additives (JECFA No. 1230) concluded that the substance does not present a safety concern at current levels of intake when used as a flavouring agent.
1.10 Farnesol has an International Fragrance Association standard – see Section 4.4.1 for details (IFRA, 2007).

2. Physical properties

2.1 Physical form: colorless, oily liquid with mild, delicate, sweet-oily odor.
2.2 Flash point: 200 °F; CC.
2.3 Log K_{ow} (calculated): 5.77.
2.4 Refractive index: 1.48.
2.5 Specific gravity: 0.89.
2.6 Vapor pressure (calculated): < 0.001 mm Hg at 20 °C.

3. Usage (Table 1)

Farnesol is a fragrance ingredient used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. Its use worldwide is in the region 1–10 metric tonnes per annum.

The maximum skin level that results from the use of farnesol in formulae that go into fine fragrances is defined by the IFRA Standard (IFRA, 2007) for this material. The recently revised standard is based on the dermal sensitization quantitative risk assessment (QRA) approach for fragrance ingredients (QRA Expert Group, 2006). The details of the standard can be found in Section 4.4.1 of this Fragrance Material Review.

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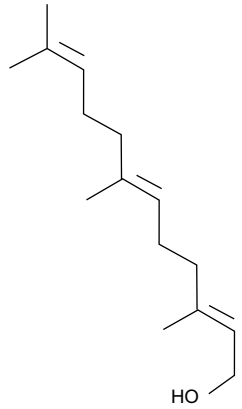

Fig. 1. Farnesol.

4. Toxicology data

4.1. Acute toxicity (Table 2)

4.1.1. Oral studies

4.1.1.1. Farnesol was evaluated for acute oral toxicity by oral gavage in SPF-Wistar albino rats (5/sex/dose), at 10 or 20 ml/kg (~10 or ~20 g/kg). Clinical signs and/or mortality were observed over a 14 day period. Decreased motor activity, coordination disturbance, piloerection and diarrhea were observed approximately 20 minutes after dosing. The oral LD_{50} was determined to be > 20 ml/kg (~20 g/kg) (RIFM, 1976d).

4.1.1.2. In a study in which 10 rats received 5 g/kg of neat farnesol and were observed for fourteen days, the oral LD_{50} was determined to be > 5 g/kg. One rat died on day 5 (RIFM, 1974b).

4.1.1.3. The oral LD_{50} was determined to be > 5.0 g/kg. Ten Sprague-Dawley rats per group were dosed with 2.15 or 5.0 g/kg farnesol in 0.5% carboxymethylcellulose and 1–2% Tropfen Cremophor EL. Animals were observed for 14 days. No effects were observed at 2.15 g/kg. One animal died at 5.0 g/kg (RIFM, 1981).

4.1.1.4. An LD_{50} of 8.764 ± 0.821 g/kg was reported when farnesol was administered orally to ten CF-1 mice per dose level. Mice were observed for 72 h. The LD_{50} was calculated by the method of Miller and Tainter (1944) (RIFM, 1967).

4.1.2. Dermal studies

4.1.2.1. The acute dermal toxicity of 10% farnesol in white petrolatum was determined in WISW strain rats (5/group) with abraded or intact skin. Farnesol was applied at 5 or 15 mg/kg (0.005 or 0.015 g/kg) in Vaseline to a 8 × 5 cm area of the back of each animal. Test site was occluded with gauze and plastic film for 24 h. No effects were observed. The acute dermal LD_{50} was determined to be > 0.015 g/kg (RIFM, 1983d).

4.1.2.2. The acute dermal LD_{50} was reported to be greater than 5 g/kg based on no deaths at that dose. Ten rabbis received a single dermal application of neat farnesol at 5 g/kg. Diarrhea was observed in one (RIFM, 1974b).

4.1.3. Intraperitoneal study

4.1.3.1. The intraperitoneal LD_{50} was determined in ten mice. Mice were dosed intraperitoneally with 0.1, 0.2, 0.464, or 1.0 g/kg farnesol in 0.5% carboxymethylcellulose and 1–2% Tropfen Cremophor EL. One animal died at 0.1 g/kg, three (3/10) at 0.2 g/kg, five (5/10) at 0.464 g/kg and all animals died at 1.0 g/kg. The LD_{50} was calculated to be 0.327 g/kg (RIFM, 1981).

4.2. Skin irritation

4.2.1. Human studies (Table 3)

4.2.1.1. In a series of 11 pre-tests for a human maximization study a 48 h closed patch tests were conducted with 10 or 12% farnesol on the backs of male and female volunteers. No irritation was observed (RIFM, 1974a; 1975a,b,c,d; 1976a,b; 1977a,b; 1978).

4.2.1.2. Irritation was evaluated during the induction phase of two human repeated insult patch tests (HRIPT) conducted on 103 and 101 volunteers. Aliquots of 0.2 ml of farnesol at concentration of 5% in petrolatum were applied for 24 h under semi-occlusion using 1 × 1 absorbent pads. A total of nine 24 h applications were made over a 3 week period. No irritation was observed (RIFM, 2000a,b).

4.2.1.3. Irritation was evaluated as a part of another HIRP test conducted on 108 volunteers. A 0.2 ml aliquot of 5% farnesol in 3:1 diethyl phthalate/ethanol was applied for 24 h under occlusion using 3/4″ × 3/4″ absorbent pad. Patches were applied three times

Table 2
Summary of acute toxicity studies

Route	Species	No. animals/dose group	LD_{50}	References
Oral (gavage)	Rats	5	~20 g/kg	RIFM (1976d)
Oral	Rats	10	>5 g/kg	RIFM (1974b)
Oral	Rats	10	>5.0 g/kg	RIFM (1981)
Oral	Mice	10	8.764 g/kg	RIFM (1967)
Dermal	Rat	5	>0.015 g/kg	RIFM (1983d)
Intraperitoneal	Mice	5	0.327 g/kg	RIFM (1981)

Table 1
Calculation of the total human skin exposure from the use of multiple cosmetic products containing farnesol

Type of cosmetic product	Grams applied	Applications per day	Retention factor	Mixture/product	Ingredient/mixture[a]	Ingredient (mg/kg/day)[b]
Body lotion	8.00	0.71	1.000	0.004	1.2	0.0045
Face cream	0.80	2.00	1.000	0.003	0.6	0.0005
Eau de toilette	0.75	1.00	1.000	0.080	1.2	0.0120
Fragrance cream	5.00	0.29	1.000	0.040	1.2	0.0116
Antiperspirant	0.50	1.00	1.000	0.010	0.1	0.0001
Shampoo	8.00	1.00	0.010	0.005	5.0	0.0003
Bath products	17.00	0.29	0.001	0.020	5.0	0.0001
Shower gel	5.00	1.07	0.010	0.012	5.0	0.0005
Toilet soap	0.80	6.00	0.010	0.015	5.0	0.0006
Hair spray	5.00	2.00	0.010	0.005	1.2	0.0001
Total						0.0304

[a] Upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in these products (IFRA, 2004).
[b] Based on a 60-kg adult.