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Fragrance material review on alpha-terpineol

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ABSTRACT

A toxicologic and dermatologic review of alpha-terpineol when used as a fragrance ingredient is presented.

Introduction

In 2006, a complete literature search was conducted on alpha-terpineol. 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 More details have been provided for unpublished data.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 When Used as Fragrance Ingredients (Belsito et al., 2008) for an overall assessment of this material.

1. Identification (Fig. 1)

1.1 Synonyms: 3-Cyclohexene-1-methanol; α,α-4-Trimethyl; 1-*p*-Menthen-8-ol; *p*-Menth-1-en-8-ol (isomer unspecified); 1-Methyl-4-isopropyl-1-cyclohexen-8-ol; α-Terpilenol; α-Terpineol; Terpineol Schlechthin.
1.2 CAS Registry Number: 98-55-5.
1.3 EINECS Number: 202-680-6.
1.4 Formula: $C_{10}H_{18}O$.
1.5 Molecular weight: 154.25.

2. Physical properties

2.1 Physical description: Colorless, slightly viscous liquid with floral, sweet, lilac-type odor.
2.2 Flash point: 191 °F; CC.
2.3 Boiling point: 218 °C.
2.4 Melting point: 10–30 °C.
2.5 Henry's law (calculated): 0. 0000158 atm m^3/mol 25 °C.
2.6 LogK_{ow} (calculated): 3.33.
2.7 Specific gravity: 0.932.
2.8 Vapor pressure (calculated): 0.02 mm Hg 20 °C.
2.9 Water solubility: 371.7 mg/l at 25 °C.
2.10 Council of Europe (COE): alpha-Terpineol was included by the COE in the list of substances granted A – may be used in foodstuffs (COE No. 62) (Council of Europe, 2000).
2.11 Food and Drug Association (FDA): alpha-Terpineol was approved by the FDA as a flavor (21 CFR 172.515).
2.12 Flavor and Extract Manufacturers Association (FEMA): Recognized as Safe as a flavor ingredient – GRAS 3 (3045) (FEMA, 1965).
2.13 Joint Expert Committee on Food Additives (JECFA): The FAO/WHO JECFA concluded that the substance does not present a safety concern at current levels of intake when used as a flavouring agent (JECFA No. 366) (JECFA, 1999).

3. Usage

alpha-Terpineol 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 of 100–1000 metric tonnes per annum.

The maximum skin level that results from the use of alpha-terpineol in formulae that go into fine fragrances has been reported to be 5.7% (IFRA, 2004), assuming use of the fragrance oil at levels up to 20% in the final product. The 97.5 percentile use level in formulae for use in cosmetics in general has been reported to be 2.85% (IFRA, 2004), which would result in a conservative calculated maximum daily exposure on the skin of 0.0726 mg/kg for high end users of these products (see Table 1).

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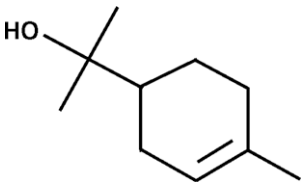

Fig. 1. alpha-Terpineol.

4. Toxicology data

4.1. Acute toxicity

See Table 2.

4.1.1. Oral studies

4.1.1.1. alpha-Terpineol was evaluated for toxicity in mice. It was administered orally *(p.o)* to 10 male dd-K mice weighing 25 g. The animals were observed for 7 days. The calculated LD_{50} was determined to be 2.9 g/kg with 95% C.I. 2.3–3.3 g/kg (Yamahara et al., 1985).

4.1.2. Intraperitoneal studies

4.1.2.1. A range finding study was conducted in Sprague–Dawley rats (2/sex/dose), prior to an associated intraperitoneal LD_{50} study. The animals were dosed at 0.050, 0.160, 0.5, 1.6, and 2 g/kg with 100% alpha-terpineol in corn oil. All the animals were observed at 1, 3, and 6 h after dosing and thereafter once daily until 72 h. All animals dosed with 1.60 and 2 g/kg test materials were found dead at 1-hour post-dose. Abnormalities in the abdominal cavity, urinary bladder, adrenals, and bright reddish lungs were noted in the dead animals (RIFM, 1984a).

4.1.2.2. Fifty (5/sex/dose) Sprague–Dawley rats, received a single intraperitoneal dose of 100% alpha-terpineol in corn oil at the doses of: 0.44, 0.61, 0.84, 1.18, and 1.64 g/kg/body weight. The animals were observed at 1, 3, and 6 h after dosing, and once daily thereafter for 14 days. The LD_{50} in males was calculated to be 0.895 g/kg (95% C.I. 0.69 and 1.15 g/kg) The LD_{50} in females was calculated to be 0.80 g/kg (95% C.I. 0.620 and 1.03 g/kg). The combined LD_{50} in males and females was calculated to be 0.847 g/kg (95% C.I. 0.70 and 1.01 g/kg) (RIFM, 1984a).

4.1.2.3. In a preliminary screen conducted prior to a carcinogenesis assay, groups of 5 male A/He mice received 24 intraperitoneal injections of alpha-terpineol in tricaprylin over a 20-week period. The animals were then observed for delayed toxicity over a 1- to 2-month period. The maximum tolerated dose (MTD) of alpha-terpineol was determined to be 0.400 g/kg (Stoner et al., 1973).

4.1.3. Intramuscular studies

4.1.3.1. Ten mice per dose received intramuscular injections of alpha-terpineol at dose levels: 4, 6, 8, 10, and 12 g/kg/bodyweight. The animals were observed for 48 h. The LD_{50} was calculated to be 2 g/kg (Northover and Verghese, 1962).

4.2. Skin irritation

4.2.1. Human studies

4.2.1.1. The irritation potential of alpha-terpineol was determined in a 4-hour human patch test. A 0.2 ml sample of neat alpha-terpineol was applied to a 25 mm Hill Top Chambers® containing a Webril® pad which was then applied to the skin of the upper outer arm of 30 volunteers for up to 4 h. alpha-Terpineol was applied progressively from 15 and 30 minutes through 1, 2, 3, and 4 h. Each progressive application (0.2 ml sample of neat alpha-terpineol was placed on a new skin site. Sodium dodecyl sulfate (SDS) at 20% was the positive control. The reactions were assessed at 24, 48, and 72 h after patch removal. When reactions were greater than or similar to SDS reactions, alpha-terpineol was determined to be irritant and when reactions were less than the SDS reactions the alpha-terpineol was non-irritant. No (0/30) irritation reactions were observed (Basketter et al., 2004).

4.2.2. Animal studies

See Table 3.

4.2.2.1. Series of 4-hour semi-occlusive patch tests were conducted on groups of 3–4 female New Zealand albino rabbits using alpha-terpineol at concentrations: 50% in diethyl phthalate (DEP) and 100% (neat). A 0.5 ml aliquot of alpha-terpineol was applied to a 2.5 cm^2 surgical lint B.P. which was then placed onto 6 cm^2 clipped intact area of the dorsal skin. Four hours later the patches were removed and additional reactions were assessed at 1, 24, 48, and 72 h. No irritation was observed at 50% in DEP. slight to moderate irritation was observed at 100% (RIFM, 1984b, 1985, 1986).

4.2.2.2. The dermal irritancy potential of alpha-terpineol was assessed in male Wistar rats weighing 160–190 g. The animals were clipped free of abdominal hair. A 2% concentration of alpha-terpineol in a gel containing 2% carboxyvinyl polymer, 2.5% triethanolamine, and 50% ethanol (EtOH) in water was placed in glass cells (16 mm inner diameter and 10 mm height). The glass cells were attached to the shaved skin with adhesives, and the ointments were removed after 10 h. A 1 cm^2 sample of skin was taken from two of the dosing sites. The excised skin was fixed in 10% neutral

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

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	2.85	0.0108
Face cream	0.80	2.00	1.000	0.003	2.85	0.0023
Eau de toilette	0.75	1.00	1.000	0.080	2.85	0.0285
Fragrance cream	5.00	0.29	1.000	0.040	2.85	0.0276
Antiperspirant	0.50	1.00	1.000	0.010	2.85	0.0024
Shampoo	8.00	1.00	0.010	0.005	2.85	0.0002
Bath products	17.00	0.29	0.001	0.020	2.85	0.0000
Shower gel	5.00	1.07	0.010	0.012	2.85	0.0003
Toilet soap	0.80	6.00	0.010	0.015	2.85	0.0003
Hair spray	5.00	2.00	0.010	0.005	2.85	0.0002
Total						0.0726

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