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Fragrance material review on myrtenol

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ABSTRACT

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

Introduction

In 2006, a complete literature search was conducted on myrtenol. 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 More details have been provided for unpublished data.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 Terpene Alcohols (Belsito et al., 2008) for an overall assessment of this material.

1. Identification (Fig. 1)

1.1 Synonyms: bicyclo[3.1.1]hept-2-ene-2-methanol, 6,6-dimethyl-;6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-methanol; 6,6-dimethyl-2-oxymethylbicyclo(1.1.3)hept-2-ene; (−)-pin-2-ene-10-ol; 2-pinen-10-ol.
1.2 CAS registry number: 515-00-4.
1.3 EINECS number: 208-193-5.
1.4 Formula: $C_{10}H_{16}O$.
1.5 Molecular weight: 152.24.
1.6 JECFA: The Joint FAO/WHO Expert Committee on Food Additives (JECFA No. 981) concluded that the substance does not present a safety concern at current levels of intake when used as a flavoring agent (JECFA, 2002).
1.7 Flavor and Extract Manufacturers' Association: Generally Recognized as Safe as a flavor ingredient – GRAS 8. (3439) (FEMA, 1965).

2. Physical properties

2.1 Physical description: a clear, almost colorless, liquid with a warm woody, herbaceous odor.
2.2 Boiling point: 224 °C.
2.3 Flash point: >200 °F; CC (FMA).
2.4 Flash point: 94 °C(201 °F) (RIFM).
2.5 Acid value: 0.05.
2.6 Log K_{ow} (calculated): 2.8.
2.7 Specific gravity: 0.978–0.983.
2.8 Vapor pressure (calculated): 0.006 mm Hg 20 °C.
2.9 Water solubility (calculated): 426.9 mg/l at 25 °C.
2.10 Henry's law: 0.00000696 atm m^3/mol 25 °C.
2.11 Refractive index: 1.496–1.497.

3. Usage (Table 1)

Myrtenol 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 <0.1 metric tonnes per annum.

The maximum skin level in formulae that go into fine fragrances has been reported to be 0.014% (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 0.13% (IFRA, 2004), which would result in a maximum daily exposure on the skin of 0.0033 mg/kg for high end users of these products.

4. Toxicology data

4.1. Acute toxicity

4.1.1. Oral studies

4.1.1.1. The acute oral toxicity of myrtenol was investigated in Sprague-Dawley rats using the ATC (acute-toxic-class) method.

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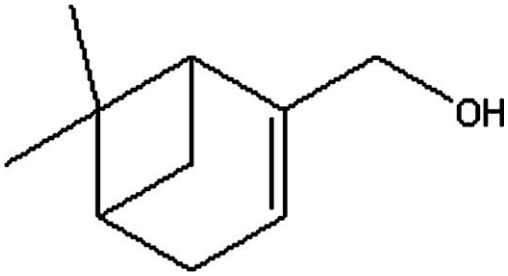

Fig. 1. Myrtenol.

Myrtenol was administered orally via gavage at 2 g/kg/body weight to 5 rats/sex. Observations were conducted before and immediately, 5, 15, 30, and 60 minutes, as well as 3, 6, and 24 h after dosing. Death occurred in 2/5 male and 5/5 female animals. Hence, three animals were tested with neat myrtenol at 0.2 g/kg. No effects were observed at this dose. At 2 g/kg, reduced motility, tremor, abdominal position and pilo-erection were the symptoms observed in one to five male and three to five female animals between 5 minutes and 1 day after dosing. Also an increase in body weight was observed in the male animals. The LD_{50} was determined to be 2.45 g/kg (in males), 0.63 g/kg (in females), and 1.4 g/kg (males and females combined). This study was conducted according to EC guideline L248:B.1 Tris and OECD guideline 423 (RIFM, 2001).

4.1.2. Intravenous studies

4.1.2.1. A mixture of myrtenol, myrtenal, pinocarveol, verbenone and verbenol, each at 1 mg was administered intravenously to hybrid rabbits. Reduced, mucus deposition and increase of muscus secretolysis and cilia-mediated mucus transport was observed. No ultrastructural defects were observed on examination of the respiratory tract (Zanker, 1983).

4.2. Skin irritation

4.2.1. Human studies (Table 2)

4.2.1.1. Two separate maximization pre-tests were carried out with 8% myrtenol in petrolatum. Patches were applied to normal sites on the backs of two groups of 24 and 26 male and female volunteers for 48 h under occlusion. No irritation was observed (RIFM, 1985, 1986).

4.2.1.2. Two separate maximization pre-tests were carried out with 8% myrtenol in petrolatum. Patches were applied to normal sites on the backs of 26 and 23 male and female volunteers for 48 h under occlusion. No irritation was observed in pre-test. Two irritation reactions (2/26) were observed in the maximization test and (1/23) irritation reaction in maximization test (RIFM, 1986, 1987a).

Table 2
Summary of irritation studies in humans

Test method	Test concentration	Results	References
Pre-test maximization	8% in petrolatum	No irritation	RIFM (1985)
Pre-test maximization	8% in petrolatum	No irritation	RIFM (1986, 1987a)
Pre-test maximization	8% in petrolatum	Slight irritation (1/23)	RIFM (1986)

4.2.1.3. Using the above method, maximization pre-test was conducted with 8% myrtenol in petrolatum on 23 male and female volunteers. One (1/23) slight irritation reaction was observed (RIFM, 1987a).

4.2.1.4. Using the above method, maximization pre-test was conducted with 8% myrtenol in petrolatum on 24 male and female volunteers. No irritation reaction was observed (RIFM, 1987a).

4.2.2. Animal studies (Table 3)

4.2.2.1. Prior to the induction phase of the associated Buehler study, a primary irritation test was carried out in Hartley albino guinea pigs (4/sex). The backs of all animals were clipped with electrical clippers. Patches were moistened with 0.3 ml of 100% (neat), 50%, 25%, 10%, 5%, 2.5%, 1.0% and 0.5% myrtenol w/v in 80% ethanol and applied for 6 h under occlusion using 25 mm hill-top chambers. Irritation was observed at 100%, 50%, 25%, 10%, and 5% concentrations w/v. No irritation was observed at 2.5–0.5% w/v myrtenol (RIFM, 1987b).

4.2.2.2. As part of the above study, using the same method as above another primary irritation test was conducted. Myrtenol at concentrations: 75%, 50%, 25%, 10%, 5%, 2.5%, 1.0% and 0.5% w/v in DEP (diethyl phthalate) was tested on guinea pigs, 4/sex. Irritation reactions were observed at 75%, 50% and 25% w/v in diethyl phthalate. No irritation was observed at 10–0.5% myrtenol w/v (RIFM, 1987b).

4.3. Mucous membrane (eye) irritation

No data available on this material.

4.4. Skin sensitization

4.4.1. Human studies

4.4.1.1. Induction studies. See Table 4.

4.4.1.1.1. Two separate maximization tests were carried out with 8% (5520 μg/cm^2) myrtenol in petrolatum on 24 and 23 male

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

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	0.13	0.0005
Face cream	0.80	2.00	1.000	0.003	0.13	0.0001
Eau de toilette	0.75	1.00	1.000	0.080	0.13	0.0013
Fragrance cream	5.00	0.29	1.000	0.040	0.13	0.0013
Antiperspirant	0.50	1.00	1.000	0.010	0.13	0.0001
Shampoo	8.00	1.00	0.010	0.005	0.13	0.0000
Bath products	17.00	0.29	0.001	0.020	0.13	0.0000
Shower gel	5.00	1.07	0.010	0.012	0.13	0.0000
Toilet soap	0.80	6.00	0.010	0.015	0.13	0.0000
Hair spray	5.00	2.00	0.010	0.005	0.13	0.0000
Total						0.0033

[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.