



Fragrance material review on *l*-menthol

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ABSTRACT

A toxicologic and dermatologic review of *l*-menthol when used as a fragrance ingredient is presented.
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Introduction

In 2006, a complete literature search was conducted on *l*-menthol. On-line 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 More details have been provided for unpublished data.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 Risk 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: cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1 α ,2 β ,5 α)]-; 3-hydroxy-*p*-menthane; *l*-4-isopropyl-1-methylcyclohexan-3-ol; *l*-3-*p*-menthanol; menthol Laevo Std; *p*-methan-3-ol; *p*-methan-3-ol; 5-methyl-2-(1-methylethyl)cyclohexanol.
- 1.2 CAS registry number: 2216-51-5.
- 1.3 EINECS number: 218-690-9.
- 1.4 Formula: C₁₀H₂₀O.
- 1.5 Molecular weight: 156.27.

2. Physical properties

- 2.1 Flash point: 196 °F; CC.
- 2.2 Boiling point: 216 °C.

- 2.3 Log *K*_{ow} (calculated): 3.38.
- 2.4 Henry's law: 0.0000152 atm m³/mol 25 °C.
- 2.5 Melting point: 43 °C.
- 2.6 Vapor pressure (calculated): 0.02 mm Hg 20 °C.
- 2.7 Water solubility (calculated): 434.5 mg/l @ 25 °C.

3. Usage

l-Menthol 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 to 1000 metric tonnes per annum.

The maximum skin level that results from the use of *l*-menthol in formulae that go into fine fragrances has been reported to be 0.58% (IFRA, 2006), 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 0.4% (IFRA, 2006), which would result in a conservative calculated maximum daily exposure on the skin of 0.0102 mg/kg/day for high end users of these products (see Table 1).

4. Toxicology data

4.1. Acute toxicity

See Table 2.

4.1.1. Oral studies

4.1.1.1. A single oral gavage dose of 10–20% *l*-menthol in olive oil was administered to mice (10/dose). The dose levels were 2.0 and 4.0 mg/g. Death occurred in 2/10 animals at 2.0 g/kg and in 7/10 animals at 4.0 g/kg. The LD₅₀ was determined to be 3.4 g/kg (Wokes, 1932).

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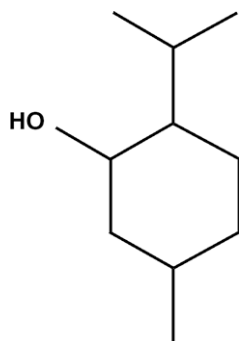


Fig. 1. *l*-Menthol.

4.1.1.2. Male mice received *l*-menthol in olive oil by oral administration. Lethargy was noted at 1.40 g/kg. The study was done to evaluate the psychotropic effects of menthol (LeBourhis and Soenen, 1973).

4.1.1.3. In summary, the acute oral LD₅₀ ranged from 0.94 to 3.18 g/kg in rats and from 2.65 to 4.38 g/kg in mice (LeBourhis and Soenen, 1973).

4.1.2. Dermal studies

4.1.2.1. Ten rabbits received a single dermal application of *l*-menthol at the dose of 5.0 g/kg/body weight. Observations were made for 14 days. No mortality or clinical signs were observed during the 14-day observation period. The LD₅₀ was determined to be greater than 5.0 g/kg based on 0/10 deaths at that dose (RIFM, 1974a).

4.1.3. Inhalation studies

4.1.3.1. Acute toxicity of *l*-menthol in the rat olfactory bulb was investigated following inhalation exposure for 11 weeks. Three Wistar rats, approximately 2 weeks old, weighing 28–39 g were placed in cylindrical Lucite cages. Fresh air was blown into the cages through charcoal filters and molecular sieves. Air flow was maintained at about 0.6 l/s through each cage. *l*-Menthol was introduced into the air stream at the concentration of 1.6×10^{-13} M. Control animals were exposed to filtered fresh air only. The rats were sacrificed after 4 and 11 weeks of exposure. Distribution of selective changes in the mitral cells of olfactory bulbs was examined and compared to controls. *l*-Menthol exposure produced moderate to severe degeneration of the mitral cells in various sections of the olfactory bulb (Pinching and Doving, 1974).

4.1.4. Intraperitoneal studies

4.1.4.1. A 333 mg/kg dose of *l*-menthol was administered to mice followed by a 14-day observation period. Liver and kidney glucuronidase levels increased after 24 h and 7 days, respectively,

Table 2
Summary of acute toxicity studies

Route	Species	No. Animals/dose group	LD ₅₀ (g/kg)	References
Oral (gavage)	Mouse	10	3.4 g/kg	Wokes (1932)
Dermal	Rabbit	10	>5 g/kg	RIFM (1974b)

compared to untreated controls. Liver damage including hypertrophy and necrosis was most significant after 24 h with near complete recovery at 14 days. Kidney changes were less severe and seen by day 3 with complete recovery by day 14 (Levvý et al., 1948).

4.1.4.2. The lethal doses in rats from an injection of a 5% solution of *l*-menthol in oil were 1.5 mg/g. The signs of toxicity after dosing were excitation followed by depression and coma (Macht, 1939).

4.1.4.3. The lethal doses in mice from an injection of a 5% solution of *l*-menthol in oil were 2.0 mg/g. The signs of toxicity after dosing were excitation followed by depression and coma (Macht, 1939).

4.1.4.4. An oily solution of *l*-menthol caused mortality in guinea pigs at a dose of approximately 4.0 mg/g (Macht, 1939).

4.1.4.5. Male mice received *l*-menthol in olive oil by intraperitoneal administration. Lethargy was seen at 0.43 g/kg. The study was done to evaluate the psychotropic effects of menthol (LeBourhis and Soenen, 1973).

4.1.5. Intravenous studies

4.1.5.1. The lethal dose in cats of a 0.1% solution of *l*-menthol in alcohol was 34 mg/kg [no further details reported] (Macht, 1939).

4.2. Skin irritation

4.2.1. Human studies

4.2.1.1. In an irritation screen for a maximization test, *l*-menthol at 8% in petrolatum was applied under occlusion to the backs of 24 volunteers for 48 h. No irritation was observed (RIFM, 1974a).

4.2.2. Animal studies

4.2.2.1. In the primary irritation phase of a Draize sensitization study, four guinea pigs were exposed to a range of concentrations of *l*-menthol either topically or intradermally. The sites were examined 24 h after application. A concentration of 10% *l*-menthol applied topically resulted in no irritation. An intradermal injection of 0.1% *l*-menthol caused slight but perceptible erythema with no edema (Sharp, 1978).

Table 1

Calculation of the total human skin exposure from the use of multiple cosmetic products containing *l*-menthol

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	0.4	0.0015
Face cream	0.80	2.00	1.000	0.003	0.4	0.0003
Eau de toilette	0.75	1.00	1.000	0.080	0.4	0.0040
Fragrance cream	5.00	0.29	1.000	0.040	0.4	0.0039
Anti-perspirant	0.50	1.00	1.000	0.010	0.4	0.0003
Shampoo	8.00	1.00	0.010	0.005	0.4	0.0000
Bath products	17.00	0.29	0.001	0.020	0.4	0.0000
Shower gel	5.00	1.07	0.010	0.012	0.4	0.0000
Toilet soap	0.80	6.00	0.010	0.015	0.4	0.0000
Hair spray	5.00	2.00	0.010	0.005	0.4	0.0000
Total						0.0102

^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.

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