Food and Chemical Toxicology 46 (2008) S64–S67

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Fragrance material review on (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate

S.P. Bhatia *, L. Jones, C.S. Letizia, A.M. Api

Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, N.J. 07677, USA

ARTICLE INFO

Keywords:
Fragrance material
Review
(3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate

ABSTRACT

A toxicologic and dermatologic review of (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate when used as a fragrance ingredient is presented.

Contents

Introduction . . . S64
1. Identification (Fig. 1) . . . S65
2. Physical properties . . . S65
3. Usage . . . S65
4. Toxicology data . . . S65
4.1. Acute toxicity . . . S65
4.1.1. Oral studies . . . S65
4.1.2. Dermal studies . . . S65
4.2. Skin irritation . . . S65
4.2.1. Human studies . . . S65
4.2.2. Animal studies . . . S66
4.3. Mucous membrane (eye) irritation . . . S66
4.4. Skin sensitization . . . S66
4.4.1. Human studies . . . S66
4.4.2. Animal studies . . . S66
4.5. Phototoxicity and photoallergy (see Table 4) . . . S66
4.5.1. Phototoxicity . . . S66
4.5.2. Photoallergy . . . S66
4.6. Absorption, distribution and metabolism . . . S66
4.7. Repeated dose toxicity . . . S66
4.8. Reproductive and developmental toxicity . . . S66
4.9. Mutagenicity and genotoxicity . . . S66
4.10. Carcinogenicity . . . S66
Conflict of interest statement . . . S67
References . . . S67

Introduction

In 2007, a complete literature search was conducted on of (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-meth-

* Corresponding author. Tel.: +1 201 689 8089; fax: +1 201 689 8070.
E-mail address: sbhatia@rifm.org (S.P. Bhatia).

0278-6915/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.fct.2008.09.015

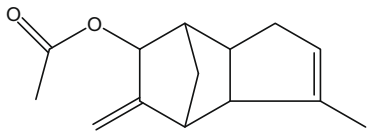

Fig. 1. (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-Hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate.

ylene-4,7-methano-1H-inden-6-yl acetate. 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. 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 Acetates (Belsito et al., 2008) for an overall assessment of this material .

1. Identification (Fig. 1)

1.1 Synonyms: 4,7-Methano-1H-inden-6-ol, 3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-, acetate, (3aα,4α,6α,7a).
1.2 CAS Registry Number: 81836-13-7.
1.3 EINECS Number: 279-836-5.
1.4 Formula: $C_{14}H_{18}O_2$.
1.5 Molecular Weight: 218.96.

2. Physical properties

2.1 Log K_{ow} (calculated): 3.81.
2.2 Water Solubility (calculated): 19.78 mg/l at 25 °C.
2.3 Henry's Law (calculated): 0.00031 atm m^3/mol at 25 °C.
2.4 Vapor pressure (calculated): 0.00247 mm Hg at 25 °C.

3. Usage

(3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-Hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate is a fragrance ingredient used in many fragrance compounds. It may be found in fragrances 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 less than 0.1 metric tonnes per annum.

The maximum skin level that results from the use of (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate in formulae that go into fine fragrances has not been reported. A default value of 0.02% is used, 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 not been reported. As such the default value of 0.02% is used to calculate the maximum daily exposure on the skin of 0.0005 mg/kg 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. Ten healthy male Wistar albino rats/group received single oral doses of (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate at 5.0 g/kg. The animals were observed for 14 days. One animal died at day 6. The clinical signs included prostration, piloerection, diarrhea, lethargy, ptosis, and anogenital area wet and stained yellow. The oral LD_{50} exceeded 5 g/kg (RIFM, 1982a).

4.1.2. Dermal studies

4.1.2.1. The acute dermal LD_{50} in rabbits exceeded 2.0 g/kg, based on 0/6 deaths at that dose. Six healthy albino rabbits received single 24-hour dermal applications of neat (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate. Observations were made for 14 days. Clinical signs included diarrhea and few feces (RIFM, 1982b).

4.2. Skin irritation

4.2.1. Human studies

4.2.1.1. Irritation was evaluated during the induction phase of a human repeated insult patch test (HRIPT). Aliquots of 0.2 ml of 20% (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate in petrolatum were applied to the upper arms of 50 volunteers (10 male and 40 females). The test sites were covered with a semi-occlusive covering of gauze and loosely applied Dermical tape. A total of nine 24 h applications were made over a 3 week period. No irritation reactions were observed (RIFM, 1982c).

Table 1
Calculation of the total human skin exposure from the use of multiple cosmetic products containing (3aα,4α,6α,7α,7aα)-3a,4,5,6,7,7a-hexahydro-3-methyl-5-methylene-4,7-methano-1H-inden-6-yl acetate

Type of cosmetic product	Grams applied	Applications per day	Retention factor	Mixture/product	Ingredient/**m**ixture[a]	Ingredient mg/kg/day[b]
Body lotion	8.00	0.71	1.000	0.004	0.02	0.0001
Face cream	0.80	2.00	1.000	0.003	0.02	0.0000
Eau de toilette	0.75	1.00	1.000	0.080	0.02	0.0002
Fragrance cream	5.00	0.29	1.000	0.040	0.02	0.0002
Antiperspirant	0.50	1.00	1.000	0.010	0.02	0.0000
Shampoo	8.00	1.00	0.010	0.005	0.02	0.0000
Bath products	17.00	0.29	0.001	0.020	0.02	0.0000
Shower gel	5.00	1.07	0.010	0.012	0.02	0.0000
Toilet soap	0.80	6.00	0.010	0.015	0.02	0.0000
Hair spray	5.00	2.00	0.010	0.005	0.02	0.0000
Total						0.0005

[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.