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Review

Addendum to Fragrance material review on Nerolidol (isomer unspecified)

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ABSTRACT

An addendum to the toxicologic and dermatologic review of Nerolidol (isomer unspecified) when used as a fragrance ingredient is presented.

Contents

Introduction

This document provides a comprehensive summary of the toxicologic review of Nerolidol when used as a fragrance ingredient including all human health endpoints. Nerolidol (see Fig. 1; CAS Number 7212-44-4) is a fragrance ingredient used in cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. Its worldwide use is greater than 10–100 metric tons per year (IFRA, 2004). It is a clear pale yellow to yellow liquid having a faint floral odor reminiscent of rose and apple (Arctander, 1969). This material has been reported to occur in nature.

In 2007, a complete literature search was conducted on Nerolidol. On-line databases that were surveyed included Chemical Abstract Services and the National Library of Medicine. In addition, fragrance companies were asked to submit all test data.

The safety data on this material was last reviewed by Opdyke (1975). All relevant references are included in this document. More details have been provided for unpublished data. The number of animals, sex and strain are always provided unless they are not given in the original report or paper. Any papers in which the vehicles and/or the doses are not given have not been included in this review. In addition, diagnostic patch test data with fewer than 100 consecutive patients have been omitted.

Nerolidol is a member of the fragrance structural group Alcohols Branched Chain Unsaturated. Their common characteristic structural elements are one hydroxyl group per molecule, a C_4–C_{16} carbon chain with one or several methyl or ethyl side chains and up to four non-conjugated double bonds. This individual Fragrance Material Review is not intended as a stand-alone document. Please refer to A Safety Assessment of Alcohols with Unsaturated Branched Chain When Used as Fragrance Ingredients (Belsito et al., 2010) for an overall assessment of this material.

1. Identification

1.1. Synonyms: 1,6,10-dodecatrien-3-ol, 3,7,11-trimethyl-; melaleucol; methylvinyl homogeranyl carbinol; peruviol; 3,7,11-trimethyl-1,6,10-dodecatrien-3-ol; 3,7,11-trimethyldodeca-1,6,10-trien-3-ol,mixed isomers;
1.2. CAS registry number: 7212-44-4;
1.3. EINECS number: 230–597;
1.4. Formula: $C_{15}H_{26}O$;
1.5. Molecular weight: 222.37;

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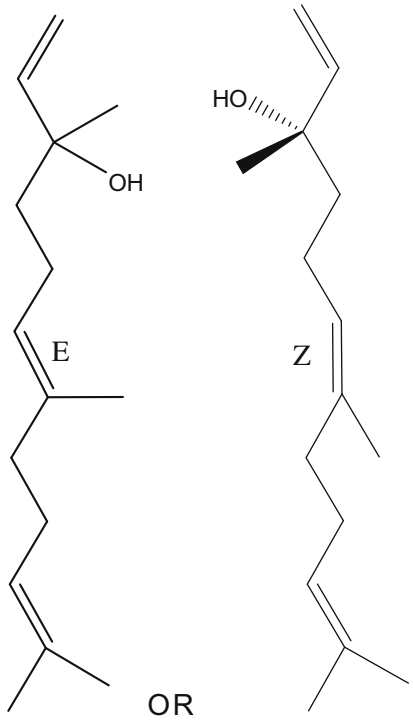

Fig. 1. Nerolidol (isomer unspecified).

1.6. Council of Europe (2000): Nerolidol (isomer unspecified) was included by the Council of Europe in the list of substances granted B – information required – 28 days oral study (COE No. 67);
1.7. FDA: Nerolidol (isomer unspecified) was approved by the FDA as GRAS (21 CFR 172.515);
1.8. FEMA (1970): Flavor and Extract Manufacturers' Association states: generally recognized as safe as a flavor ingredient – GRAS 3.

2. Physical properties

2.1. Physical form: a clear pale yellow to yellow liquid having a faint floral odor reminiscent of rose and apple;
2.2. Boiling point: 276 °C;
2.3. Flash point:>212 °F; CC;
2.4. Henry's Law (calculated): 0.000181 atm m^3/mol 25 °C;
2.5. Log K_{ow} (calculated): 5.68;
2.6. Refractive index: 1.4799;
2.7. Refractive index @ 20 °C: 1.478–1.483;
2.8. Specific gravity: 0.872–0.882 (20 °C);
2.9. Specific gravity: 0.870–0.880 (25 °C);
2.10. Vapor pressure (calculated): 0.1 mm Hg 20 °C;
2.11. Water solubility (calculated): 1.532 mg/l @ 25 °C;
2.12. UV spectra available at RIFM, peaks at 220–230 and returns to base line at 340.

3. Usage

Nerolidol (isomer unspecified) 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 in the region of 10–100 metric tons per annum (IFRA, 2004).

The average maximum use level in formulae that go into fine fragrances has been reported to be 2.02% (IFRA, 2007), 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 1.15 (IFRA, 2007), which would result in a maximum daily exposure on the skin of 0.0293 mg/kg for high end users (see Table 1).

4. Toxicology data

4.1. Absorption, distribution and metabolism

4.1.1. Metabolism

In vivo studies.

Rats were fed 20, and 40 mg of Nerolidol mixed with 1 mL of cottonseed oil and 30–35 mL of evaporated milk per day, for a period of 8 days. The average daily excretion on the 1st to 4th and 4th to 8th day was monitored. Respectively, 20 mg/day yielded 0.3 and 0.7 mg with a maximum average of 0.9 mg. From 40 mg/day a maximum average of 2.1 mg was determined and the average daily excretions were 1.0 and 1.6 mg/day (Longenecker et al., 1939).

In vitro studies.

Saccharomyces cerevisiae of haploid IWD72 strain was grown in a medium comprised of yeast extract, bacteriolocial peptone, glucose, adenine, and uracil. Nerolidol (100 ug ml^{-1}) in ethanol was added to the 50 ml bacteria culture in YEPD medium. After 24 h, the aerobic cultures were harvested and cells were collected. Residual Nerolidol recovered was 79.6 ug ml^{-1} (King and Dickenson, 2003).

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

Product type	Grams applied	Applications per day	Retention factor	Mixture/product	Ingredient/mixture[a]	Ingredientmg/kg/day[b]
Anti-perspirant	0.5	1	1	0.01	1.15	0.0010
Bath products	17	0.29	0.001	0.02	1.15	0.0000
Body lotion	8	0.71	1	0.004	1.15	0.0044
Eau de toilette	0.75	1	1	0.08	1.15	0.0115
Face cream	0.8	2	1	0.003	1.15	0.0009
Fragrance cream	5	0.29	1	0.04	1.15	0.0111
Hair spray	5	2	0.01	0.005	1.15	0.0001
Shampoo	8	1	0.01	0.005	1.15	0.0001
Shower gel	5	1.07	0.01	0.012	1.15	0.0001
Toilet soap	0.8	6	0.01	0.015	1.15	0.0001
Total						0.0293

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

4.2. Reproductive and developmental toxicity

To study the development of the fetal epidermal barrier, in vitro, activators of the receptors for vitamin D_3, retinoids, peroxisome proliferators activated receptors (PPARs), and farnesoid X-activated receptors (FXR) were examined. Sprague Dawley rats were impregnated (plug date = day 0) so that 17 day fetuses could be used for an organ culture model and measurement of barrier function. Specifically, the effect of FXR activators, isoprenoid precursors and metabolites on the barrier development in vitro was observed. Explants were incubated for 2 days in the presence of 100 uM Nerolidol. Full thickness flank skin from the fetal rats was excised and prepared. Skin samples were also analyzed with light and electron microscopy. Incubation of Nerolidol did not significantly affect barrier function or activate the FXR during skin development (Hanley et al., 1997).

This individual Fragrance Material Review is not intended as a stand-alone document. Please refer to A Safety Assessment of Alcohols with Unsaturated Branched Chain When Used as Fragrance Ingredients (Belsito et al., 2010) for an overall assessment of this material.

Conflict of interest statement

This research was supported by the Research Institute for Fragrance Materials, an independent research institute that is funded by the manufacturers of fragrances and consumer products containing fragrances. The authors are all employees of the Research Institute for Fragrance Materials.

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