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Final Report on the Safety Assessment of o-Cymen-5-ol

The safety on o-Cymen-5-ol has not been documented and substantiated. The Cosmetic Ingredient Review Expert Panel cannot conclude that o-Cymen-5-ol is safe for use in cosmetic products until such time that the appropriate safety data have been obtained and evaluated. The data that were available are documented in the report as well as the types of data that are required before a safety evaluation may be undertaken.

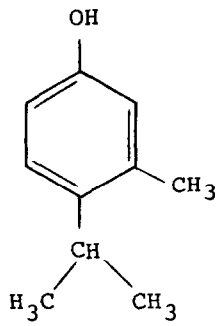
INTRODUCTION

The following report documents all of the relevant published and unpublished data available to the Cosmetic Ingredient Review (CIR) on o-Cymen-5-ol. The CIR Expert Panel reviewed these data and concluded that additional information is required to substantiate the safety of o-Cymen-5-ol for use in cosmetic products. The type of data needed to assess the safety of this cosmetic ingredient is outlined in the Discussion section of this report. Pursuant to Section 44 paragraph (c) of the CIR Procedures an Insufficient Data Report was released for a 90-day public comment period. No comments were received, nor was there commitment by any party to obtain the needed information. This Final Report is being released to document the Expert Panel's decision that there is a lack of information to make a determination whether o-Cymen-5-ol is either safe or unsafe for use as a cosmetic ingredient.

CHEMISTRY

Definition and Structure

o-Cymen-5-ol (CAS No.: 3228-02-2) is the substituted phenol that conforms to the formula:[1]



This cosmetic ingredient was first synthesized in 1954 as a homologue of thymol.[2] Additional names for the compound include: Biosol, 3-methyl-4-(1-methylethyl)phenol, 3-methyl-4-isopropylphenol, 2-isopropyl-5-hydroxytoluene, p-thymol, 4-isopropyl-m-cresol, 4-isopropyl-3-methylphenol, and 5-oxy-1-methyl-2-isopropyl-benzol.[1-4]

Properties

o-Cymen-5-ol (formula weight: 150) is a colorless, tasteless and odorless crystalline solid that is stable to light. The pH of the compound is reported to be neutral. It has a melting point of 111°–112°C, and a boiling point of 244°C. o-Cymen-5-ol absorbs UV light at a maximum of approximately 275 nm. The material is soluble in glacial acetic acid, volatile oils, fats, and benzene; it is barely soluble in water. Table 1 lists the solubilities of o-Cymen-5-ol in various solvents at 22°C.[2,4]

Kuchar et al.[5] reported that the Hansch π parameter of the 3-CH_3, 4-iso-C_3H_7 substituent of o-Cymen-5-ol is 1.58. The π parameter is defined as the log P_x − log P_H where P_x and P_H are the partition coefficients in the n-octanol-water system for substituted and unsubstituted compounds, respectively. The π parameter characterizes the contribution of the substituent to the lipophilic nature of the whole molecule, and is used as a measure of the lipophilicity in quantitative chemical structure/biological activity relationships.

Perrin et al.[6] have described the conditions under which o-Cymen-5-ol crystallizes. Data relating to the compound's infrared spectra, combustion enthalpy, and resonance energy have also been published.[7,8]

TABLE 1. Solubilities of o-Cymen-5-ol.

Solvent	*Solubility at 22°C (%)*
Water	0.014
Alcohol (99.5%)	31.0
Alcohol (91%)	10.7
Chloroform	2.5
Ether	20.0
Glycerine (85%)	0.1
Liquid paraffin	0.014

Data from Ref. 2.

Reactivity

o-Cymen-5-ol reacts readily with oxidizing agents to form methyl bridged dimers and quinone dimers.[4]

Analytical Methods

High-performance liquid chromatographic analysis has been used to determine o-Cymen-5-ol at concentrations of 2.5–12.5 ppm in various cosmetic products.[9,10] Use of gas chromatography for the analysis of this compound has also been reported.[11]

COSMETIC USE

Purpose in Cosmetics

o-Cymen-5-ol is used in cosmetic formulations as a chemical preservative.[12]

Scope and Extent of Use in Cosmetics

Data submitted to the Food and Drug Administration (FDA) in 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that o-Cymen-5-ol was used as an ingredient in a total of 55 cosmetic formulations at concentrations of ≤0.1% (Table 2).[13] Voluntary filing of such product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[14]

TABLE 2. Product Formulation Data.[a]

Product category[b]	*Total no. of formulations in product category*	*Total no. of formulations containing o-Cymen-5-ol at concentrations of ≤0.1 (%)*[b]
Eye shadow	2582	6
Mascara	397	1
Other eye makeup preparations	230	2
Makeup foundations	740	8
Nail creams and lotions	25	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4
Face, body, and hand skin care preparations (excluding shaving preparations)	823	13
Moisturizing skin care preparations	747	11
Night skin care preparations	219	8
Other suntan preparations	28	1
1981 TOTAL		55

[a] Data from Ref. 13.

[b] Preset product categories and concentration ranges are used by firms reporting data to FDA in order to conform to federal filing regulations outlined in 21 CFR 720.4.[14]

Surfaces to Which Applied

Cosmetic products containing o-Cymen-5-ol are applied to or have the potential to come in contact with eyes, skin, and nails (Table 2).[13]

Frequency and Duration of Application

Product formulations containing o-Cymen-5-ol may be used from once per week to several times per day. Many of the products may remain in contact with body surfaces for as briefly as a few minutes to as long as a few days. Each product has the potential to be applied hundreds of times over the course of several years.

NON-COSMETIC USE

o-Cymen-5-ol is commonly sold for use as an antimold and antimicrobial agent, as a preservative, and as an antioxidant.[4]

An insect-repellent composition containing o-Cymen-5-ol as a component has been described by Inazuka and Tsuchiya.[15] A number of patents have also been issued which describe the use of o-Cymen-5-ol in the preparation of other phenolic compounds, and in the stabilization of resin blends.[11,16-20]

BIOLOGY

Antimicrobial Properties

o-Cymen-5-ol demonstrates antimicrobial activity against *Pseudomonas aeruginosa, Salmonella typhosa (Bacillus typhi), Escherichia coli,* and *Staphylococcus aureus.*[21,22] The phenol coefficient of o-Cymen-5-ol is 19 for *E. coli* and 17 for *S. typhosa* and *S. aureus.*[22] The compound inhibits the growth of bacteria at concentrations of 0.01%–0.02%, and inhibits the growth of fungi and yeasts at concentrations of 0.01%–0.05%.[2]

Animal Toxicology

Acute Oral Toxicity

Ten percent o-Cymen-5-ol in an aqueous suspension of 0.5% carboxymethylcellulose was given by stomach tube to two groups of four-week old Slc-ddy mice. The sample of o-Cymen-5-ol used in the study had a purity of >99%. One group of 14 animals (seven females and seven males) received the test suspension in a dose of 10 ml/kg, whereas a similar group of 14 mice was given a dose of 22 ml/kg. Animals were given food and water ad libitum prior to the single oral dose. No change was noted in the "general condition" of the mice throughout the seven-day observation period. Females of both dosage groups and males administered 22 ml/kg showed lowered body weight gain the first day following dosing; however, weight gain was normal thereafter. Necropsy was performed eight days after dosing and no lesions were found. No deaths were noted at either dosage level. The LD_{50} of the test suspension was observed to be >22.0 ml/kg; the LD_{50} of o-Cymen-5-ol was calculated as >2.2 g/kg.[23]

Eye Irritation

The ocular irritating ability of 0.1% and 1.0% o-Cymen-5-ol in Vaseline was determined in two groups of albino rabbits (nine animals/group). The sample of o-Cymen-5-ol employed in the study had purity of >99%. One-tenth gram of the test material was instilled once into one eye of each rabbit; the other eye served as untreated control. The Vaseline vehicle was also instilled into one eye of each of three animals. The eyes of the vehicle control group received no water rinse. Eyes of the treated animals received either no water rinse (three rabbits/group) or a water rinse 2 (three rabbits/group) or 4 (three rabbits/group) sec after administration of o-Cymen-5-ol. Eye irritation was graded according to the evaluation system of Draize[24] at 1 h, 4 h, and Days 1–7 after instillation of the test substance. In the 0.1% treatment group, discharge and "barely perceptible" to "very slight" redness were observed in the conjunctivae under both rinse and no rinse conditions 1 and 24 h after treatment. This eye irritation had completely cleared by the 48 h reading. In the 1.0% treatment group, "very slight redness and discharge" occurred in the conjunctivae of the unwashed eye after 1 and 4 h; no irritation was detected by the 24 h reading. No ocular irritation was noted in the rabbits receiving the water rinse. In the vehicle control group, "very slight redness and discharge" were observed in the conjunctivae at the 1 and 4 h reading; this irritation dissipated within 24 h following treatment. It was the investigator's opinion that the ocular irritation produced by o-Cymen-5-ol was "very low."[25]

Skin Irritation

A test for primary skin irritation was conducted with 0.1% and 1.0% o-Cymen-5-ol in Vaseline on one group of eight albino rabbits. The sample of o-Cymen-5-ol used in this study had a purity of >99%. Patches containing the test materials and the Vaseline vehicle were applied to the clipped skin of each animal. Test sites on the eight animals were either abraded (four rabbits) or intact (four rabbits). After 24 h, the patches were removed and the skin reactions evaluated on a scale of 0.0 (no erythema or edema) to 8.0 (severe erythema and edema). No irritation was observed to 0.1% or 1.0% o-Cymen-5-ol on either intact or abraded skin. Barely perceptible erythema was noted at the 72 h reading on the intact skin of one rabbit as a result of exposure to the Vaseline vehicle.[26]

Eight male albino rabbits were evaluated for primary skin irritation following exposure to 5% o-Cymen-5-ol in PEG 400 (PEG-400 is a polymer of ethylene oxide that conforms to the formula $H(OCH_2CH_2)_nOH$ and where n has an average value of 400). The backs of each animal were clipped of all hair, and patches containing 0.3 ml of the test material were then applied to either intact (four rabbits) or abraded (four rabbits) skin. After 24 h, the patches were removed and the skin reactions evaluated on a scale of 0 (no erythema or edema) to 8.0 (severe erythema and edema). Skin responses were graded again after 72 h. The Primary Irritation Index (PII), a value depicting the average score of each exposure group as a whole, was 0.0/8.0 for the vehicle control animals. The PII for the 5.0% treatment group was 0.06/8.0 indicating a "very low" degree of primary skin irritation.[27]

The ability of 10% o-Cymen-5-ol in ethanol to elicit primary skin irritation was determined in three male albino guinea pigs. The test material was applied in a 0.3 ml dose every day for three days to the clipped flanks of each animal.

Following each of the three 24 h exposures, skin reactions were graded on a scale of 0 (no reaction) to 4.0 (severe erythema and edema). It was not reported whether test sites were covered with an occlusive patch, whether skin was intact and/or abraded, or whether the same sites were used for each 24 h application. The PIIs for ethanol and 10% o-Cymen-5-ol in ethanol were 0.0/4.0 and 0.22/4.0, respectively. The latter score was considered by the investigator to be indicative of a "very low" degree of primary skin irritation.[28]

Skin Sensitization

A guinea pig maximization test was conducted by means of the procedures outlined by Magnusson and Kligman[29] to determine the ability of o-Cymen-5-ol to induce skin sensitization. Induction patches containing 1.0% o-Cymen-5-ol in ethyl alcohol were applied to four groups of male guinea pigs of the Hartley strain (10 animals/group). Challenge patches consisted of either 10%, 1.0%, 0.1%, or 0.01% o-Cymen-5-ol in acetone. The number of animals exhibiting skin reactions at the challenge reading were 5/10, 2/10, 1/10, and 0/10 to 10%, 1.0%, 0.1%, and 0.01% o-Cymen-5-ol, respectively. No skin sensitization was observed in control animals given a challenge application of ethyl alcohol. The investigator concluded that o-Cymen-5-ol demonstrated "very slight allergenicity."[30]

Clinical Assessment of Safety

Skin Irritation and Sensitization

A 24 h patch test was conducted on 53 female volunteers to determine the skin irritating effects of o-Cymen-5-ol. The purity of o-Cymen-5-ol used for testing was >99%. To the forearm of each subject were applied three patches, one containing Vaseline, one containing 0.1% o-Cymen-5-ol in Vaseline, and another containing 1.0% o-Cymen-5-ol in Vaseline. Skin reactions were evaluated within 3 h following removal of the patches. No skin irritation was observed in any subject.[31]

A maximization test was conducted on 27 men to determine the ability of o-Cymen-5-ol to induce skin sensitization. The procedure used was a modification of the method described by Kligman.[32] The five materials evaluated were Vaseline (vehicle control), o-Cymen-5-ol in Vaseline, a cream base (vehicle control), o-Cymen-5-ol in cream base, and petrolatum (negative control). For each test material, a total of five 48 h induction patches were applied to the forearm at the same site. The initial induction exposure was preceded by a 24 h occlusive patch containing 5% aqueous sodium lauryl sulfate (SLS). o-Cymen-5-ol concentrations employed during the induction phase were 1.0%. Ten to fourteen days after the induction phase, challenge patches were applied to previously untreated sites for 48 h. Challenge exposures were preceded by 30 min applications of 5% aqueous SLS under occlusion to the left-hand side of the back. Challenge patches were also applied without SLS pretreatment to the right-hand side of the back. The concentration of o-Cymen-5-ol employed during the challenge phase was 0.1%. On SLS pretreated sites, "low grade irritant reactions" were observed in several individuals to each of the five substances at the 48 h challenge reading. By the 72 h reading, approximately half the subjects had low grade irritant reactions to each of the five test materials. On sites receiving no SLS treatment, no reactions were observed to any test material at either the 48 or 72 h challenge

reading. It was concluded that o-Cymen-5-ol produced no reactions that could be considered irritant or allergic in nature.[33]

DISCUSSION

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on o-Cymen-5-ol are insufficient to determine whether this ingredient, under each relevant condition of use, is either safe or not safe. The Panel released a "Notice of Insufficient Data Report" on January 7, 1983 outlining the data needed to assess the safety of o-Cymen-5-ol. The types of data required included:

1. Animal skin absorption and excretion data. If o-Cymen-5-ol is absorbed through the skin, then additional distribution and metabolism studies are necessary.
2. If skin absorption occurs, then animal teratogenesis data are necessary.
3. Mutagenicity data (battery of tests is required).
4. Subchronic and chronic oral toxicity data.
5. Human skin sensitization and photosensitization (phototoxicity and photoallergenicity) data.

There has been no response or interest by any party to supply the aforementioned information.

CONCLUSION

The safety of this ingredient has not been documented and substantiated. The CIR Expert Panel cannot conclude whether o-Cymen-5-ol is safe for use in cosmetic products until such time that the appropriate safety data have been obtained and evaluated.

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