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Final Report on the Safety Assessment of Isopropyl Isostearate

Isopropyl Isostearate, the ester of isopropyl alcohol and isostearic acid, is used as a skin conditioning agent—emollient in cosmetic products. Undiluted Isopropyl Isostearate was classified as a slight ocular irritant. Repeated applications of a 10.0% aqueous suspension of Isopropyl Isostearate to the skin of albino rabbits was well-tolerated. Based upon the safety test data on chemically similar isopropyl esters that is summarized in the report, it is concluded that Isopropyl Isostearate is safe as a cosmetic ingredient in the present practices of use and concentration.

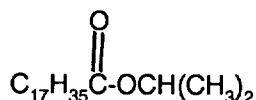
INTRODUCTION

The toxicity of Isopropyl Isostearate is reviewed in this report. A summary of the toxicity data on such chemically similar cosmetic ingredients as Isopropyl Stearate, Isopropyl Palmitate, Isopropyl Myristate, and Isopropyl Lanolate is also included as these have been reviewed previously by the CIR Expert Panel. The available safety data on these ingredients are considered to be supportive of the safety data on Isopropyl Isostearate.

CHEMISTRY

Chemical and Physical Properties

Isopropyl Isostearate (CAS Nos. 31478-84-9 and 68171-33-5), also known as Heptadecanoic Acid, 16-Methyl-, 1-Methylethyl Ester, is the ester of isopropyl alcohol and isostearic acid that conforms generally to the formula:⁽¹⁾



It is a mixture of isopropyl esters of 80% branched chain C₁₆ and C₁₈ acids and 20% straight chain C₁₄, C₁₆, and C₁₈ acids with a small amount of oleic acid.⁽²⁾ Properties of Isopropyl Isostearate are summarized in Table 1.

TABLE 1. PROPERTIES OF ISOPROPYL ISOSTEARATE⁽²⁾

Form	Liquid
Solubility	Soluble in acetone, ethyl acetate, isopropyl alcohol, and mineral oil
Specific gravity at 25°C	0.853 to 0.859
Acid value	1.0 maximum
Ester value	169.0 to 180.0
Iodine value	3.0 maximum

Analytical Methods

Isopropyl Isostearate has been analyzed via infrared spectroscopy and gas chromatography.^(2,3)

COSMETIC USE

Isopropyl Isostearate is used as a skin conditioning agent-emollient in cosmetics.⁽⁴⁾

The FDA cosmetic product formulation computer printout⁽⁵⁾ is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.⁽⁶⁾ Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. Isopropyl Isostearate is used in 78 cosmetic products at concentrations ranging from $\leq 0.1\%$ to 50.0% (Table 2).⁽⁵⁾

Isopropyl Isostearate has been approved for use as a cosmetic ingredient in Japan.⁽⁷⁾ This ingredient is not included in the list of substances that may not be used in cosmetic products marketed in countries of the European Economic Community.⁽⁸⁾

TABLE 2. PRODUCT FORMULATION DATA FOR ISOPROPYL ISOSTEARATE⁽⁵⁾

Product category	Total no of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			>25-50	>10-25	>5-10	>1-5	>0.1-1	≤ 0.1
Eye area cosmetics	1135	11	—	—	1	9	1	—
Facial makeup products	3194	40	1	7	8	19	4	1
Skin care products	3110	20	—	—	5	6	5	4
Miscellaneous other cosmetic products	2228	7	—	2	—	4	—	1
1989 TOTALS		78	1	9	14	38	10	6

Noncosmetic Use

Isopropyl Isostearate is used as a dispersing agent in aerosol formulations.⁽⁹⁾

TOXICOLOGY

Ocular Irritation

The ocular irritation potential of undiluted Isopropyl Isostearate was evaluated using six male New Zealand albino rabbits. The test substance was instilled (0.1 ml) into the conjunctival sac of one eye of each animal; eyes were not rinsed. Untreated eyes served as controls. Ocular irritation reactions were scored on days 1, 2, 3, 4, and 7 post-instillation according to the scale by Draize:⁽¹⁰⁾ 0–110. A 10% aqueous suspension of Isopropyl Isostearate was also tested. Both concentrations of Isopropyl Isostearate were classified as slight ocular irritants.⁽¹¹⁾

Skin Irritation

The skin irritation potential of undiluted Isopropyl Isostearate was evaluated using six male New Zealand albino rabbits (2.5–3.5 kg). The test substance (0.5 ml) was applied via gauze pads to the left flank (intact) and right flank (abraded) of each animal. Each pad was covered with an occlusive patch and secured with hypoallergenic adhesive plaster. Sites were scored 24 and 72 h after patch application according to the scale: 0 (no edema, erythema) to 4 (severe edema, erythema). Isopropyl Isostearate was classified as a non-irritant (Primary Irritation Index = 0.42).⁽¹¹⁾

Isopropyl Isostearate, 0.5 ml of an undiluted and a 10.0% aqueous suspension, was applied daily to the right and left flanks (shaved skin) of each of three male albino rabbits (2.5–3.5 kg) five days per week for a period of 8 weeks. Excess test substance was wiped from the skin with gauze 30 s after each application. Application sites were scored daily according to the scale: 0 (no erythema) to 4 (serious erythema with slight scar formation) and 0 (no edema) to 4 (serious edema, covering all of the treated area, or more). Scores were averaged on a weekly basis, and the maximum irritation index (IIMM) was determined at the end of the treatment period. Microscopic examination was performed on skin samples (2 per animal) that differed macroscopically. The criteria for classifying a substance as poorly tolerated after repeated applications were as follows: (1) pathologic reactions must be observed in all three animals treated, (2) pathologic reactions must appear over the entire treated surface of the epidermis, and not only at localized points, and (3) microscopic examination of two fragments of treated skin from each rabbit must confirm the macroscopic observations. Undiluted Isopropyl Isostearate was very poorly tolerated (IIMM = 3.34; treatment was discontinued after 5 weeks). Isopropyl Isostearate as a 10.0% aqueous suspension was relatively well tolerated (IIMM = 2.00).⁽³⁾

Comedogenicity

The comedogenic potential of Isopropyl Isostearate (undiluted) was evaluated using two New Zealand albino rabbits. The test substance was applied to the internal surface of the external ear daily for 2 weeks. The untreated external ear served as the control. At the end of the treatment period, reactions were scored according to the scale: 0 (no

increase in visible follicular keratosis) to 5 (the presence of more severe comedones throughout the ear). Isopropyl Isostearate induced the formation of severe comedones throughout the skin of the external ear.^(1,2)

SUMMARY OF DATA ON CHEMICALLY SIMILAR INGREDIENTS

Acute Inhalation Toxicity

Neither death nor other signs of systemic toxicity was observed in rats exposed for 1 hour to an aerosol antiperspirant containing 16 to 20% isopropyl myristate. The gravimetric ambient concentration of isopropyl myristate at the time of exposure ranged from 33 to 41 mg/L of air. Similar results were reported in a study in which albino rats were exposed to aerosolized isopropyl palmitate (200 mg/L of air) for 1 h.

Acute Oral Toxicity

The LD₅₀ was not achieved when albino rats were treated with 8 ml/kg of undiluted isopropyl stearate. When rats and mice were dosed with undiluted isopropyl myristate, the LD₅₀ was not achieved at a dose of 16 ml/kg in rats and 49.7 ml/kg in mice. Additionally, doses of 64 ml/kg of undiluted isopropyl palmitate (rats) and 64 ml/kg of undiluted isopropyl lanolate (rats) were less than the LD₅₀.

Dermal Toxicity

A dermal LD₅₀ of greater than 5 g/kg was reported in a study in which rabbits were treated with undiluted isopropyl myristate. No deaths were reported after rabbits received repeated applications of an aerosol antiperspirant containing 16 to 20% isopropyl myristate; severe skin irritation was observed. In another study, toxic effects were not observed in rabbits that received a single dermal application (2.0 ml/kg) of isopropyl palmitate, and no deaths were reported. Repeated applications of undiluted isopropyl palmitate also did not cause death. Orthokeratosis and slight acanthosis were cutaneous alterations observed in some of the rabbits tested. The repeated applications of a cosmetic foundation product containing 5% isopropyl lanolate did not induce signs of toxicity in rats.

Ocular Irritation

Undiluted isopropyl stearate did not induce ocular irritation when instilled into the conjunctival sac of New Zealand rabbits. Similar results were reported when undiluted isopropyl myristate was used. In five separate Draize ocular irritation tests, undiluted isopropyl palmitate did not cause significant ocular irritation in any of the rabbits tested. In four separate ocular irritation studies using isopropyl lanolate, the mean Draize ocular irritation scores indicated no ocular irritation or mild transient irritation.

Skin Irritation

Moderate skin irritation was observed at intact and abraded skin sites of rabbits that received a single application of undiluted isopropyl stearate. In four Draize skin

irritation tests, repeated applications of undiluted isopropyl myristate to the skin of rabbits resulted in minimal irritation; results from a fifth Draize test indicated no skin irritation. Draize test results for isopropyl palmitate indicated that it was non-irritating to slightly irritating to the skins of albino rabbits. In other Draize tests, isopropyl lanolate was non-irritating to intact and abraded skin sites of rabbits and guinea pigs.

A personal cleanliness product containing 1% isopropyl stearate was classified as a slight skin irritant after repeated applications were made to human subjects. Primary skin irritation was not observed in human subjects patch tested with undiluted isopropyl myristate. Repeated applications of this ingredient induced very slight skin irritation. In separate studies, primary skin irritation also was not observed in subjects patch tested with undiluted isopropyl palmitate or in those patch tested with undiluted isopropyl lanolate.

Skin Sensitization

Isopropyl myristate and isopropyl lanolate did not induce sensitization in guinea pigs when either was tested at a concentration of 0.1%.

Skin sensitization was not observed in human subjects patch tested with two personal cleanliness products containing 1% isopropyl stearate. In separate maximization tests, skin sensitization was not observed in human subjects patch tested using 20% isopropyl myristate in petrolatum, those patch tested using a bath formulation containing 42.9% isopropyl myristate, or a bath formulation containing 45.6% isopropyl palmitate. In other studies, sensitization reactions were not observed in human subjects patch tested with undiluted isopropyl palmitate. The results from four sensitization studies of an aerosol antiperspirant containing 52 to 58% isopropyl myristate also were negative. Sensitization reactions were observed in two of 53 subjects challenged with undiluted isopropyl lanolate. It was noted that the two subjects were hypersensitive to many substances.

PHOTOSENSITIZATION

In a photosensitization study, distilled Isopropyl Lanolate was applied to the skin of 10 male guinea pigs daily for 10 days. After each application, the skin was exposed to ultraviolet light for 6 h. There was no evidence of photosensitization.

PHOTOTOXICITY

Phototoxicity was not observed in 10 healthy human subjects after patch testing (occlusive patches) with a bath formulation containing 42.9% isopropyl myristate in one study and after testing with 45.6% isopropyl palmitate in a second study. Test sites were irradiated after 6 h and 24 h of contact. Similar negative results were reported in photocontact allergenicity studies of these bath formulations.

CARCINOGENICITY

No neoplasms were induced after 0.1 ml of a 1% solution (solvent not stated) of isopropyl myristate was applied to the skins of mice once per week for 18 weeks. In

another study, isopropyl myristate was applied to the backs of mice twice per week from the time they were 7 weeks old until death (average lifespan = approximately 80 weeks). Isopropyl myristate concentrations of 10, 50, and 100% in acetone were applied to groups of 50 animals.

SUMMARY

Isopropyl Isostearate (CAS Nos. 31478-84-9 and 68171-33-5) is the ester of isopropyl alcohol and isostearic acid. It is used as a skin conditioning agent-emollient in cosmetics at concentrations ranging from $\leq 0.1\%$ to 50.0%.

Undiluted Isopropyl Isostearate and a 10.0% aqueous suspension of Isopropyl Isostearate were classified as slight ocular irritants when instilled into the conjunctival sac of albino rabbits.

A single 24 h application, under an occlusive patch, of undiluted Isopropyl Isostearate did not cause skin irritation in albino rabbits. Repeated applications of undiluted Isopropyl Isostearate and a 10.0% aqueous suspension of Isopropyl Isostearate to the skin of albino rabbits were very poorly tolerated and relatively well tolerated, respectively. Comedones were observed in the skin of the external ear of albino rabbits that received repeated applications of undiluted Isopropyl Isostearate.

DISCUSSION

Data indicating that undiluted Isopropyl Isostearate is a skin irritant and a slight ocular irritant, and that 10.0% Isopropyl Isostearate is a slight ocular irritant, but not a skin irritant, are presented in this report. These data, along with positive comedogenicity data, are the only toxicological data available for the CIR Expert Panel's review of Isopropyl Isostearate. The Expert Panel has determined that chemically similar cosmetic ingredients, isopropyl stearate, isopropyl myristate, isopropyl palmitate, and isopropyl lanolate, are safe, at concentrations used in cosmetics.⁽¹³⁻¹⁶⁾ These ingredients, including Isopropyl Isostearate, are isopropyl esters resulting from the reaction of isopropyl alcohol with long-chain saturated aliphatic acids. Like Isopropyl Isostearate, cosmetic use concentrations of these ingredients range from $\leq 0.1\%$ to 50.0%. A collective evaluation of the data on animals summarized in this report indicates that the isopropyl esters, undiluted or at use concentrations, are relatively harmless when administered to animals in acute oral, dermal, and inhalation toxicity studies, are not significant ocular irritants, induce skin irritation reactions ranging from none to moderate, are not sensitizers or photosensitizers, and are not carcinogenic. In studies involving healthy human subjects, these esters, undiluted or at use concentrations, produced, at most, slight skin irritation but not sensitization.

Based upon chemical similarities between the isopropyl esters and similar cosmetic use concentrations, the Expert Panel determined that the data used in its safety assessments of isopropyl stearate, isopropyl myristate, isopropyl palmitate, and isopropyl lanolate can also be used in the safety assessment of Isopropyl Isostearate.

CONCLUSION

On the basis of the available animal and clinical data on isopropyl stearate, isopropyl myristate, isopropyl palmitate, and isopropyl lanolate presented in this

report, the CIR Expert Panel concludes that Isopropyl Isostearate is safe as a cosmetic ingredient in the present practices of use and concentration.

ACKNOWLEDGEMENT

This report was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst and Writer.

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