JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 11, Number 1, 1992
Mary Ann Liebert, Inc., Publishers

4

Final Report on the Safety Assessment of Isopropyl Linoleate

Isopropyl Linoleate is the ester of isopropyl alcohol and linoleic acid. In cosmetics, it is used as a skin conditioning agent and emollient at concentrations ranging from 0.1% to 10.0%.

In an acute oral toxicity study, none of the albino rabbits that received doses of 10.0% Isopropyl Linoleate in corn oil died. Isopropyl Linoleate (undiluted and 10.0% suspension) were classified as slight ocular irritants. Undiluted Isopropyl Linoleate was classified as a slight skin irritant. The report concludes that the safety of use of Isopropyl Linoleate has not been documented and substantiated, and that it is not possible to conclude that the ingredient is safe for use in cosmetic products. The report details the type of safety test data that is needed to substantiate the safety of use of Isopropyl Linoleate in cosmetic products.

INTRODUCTION

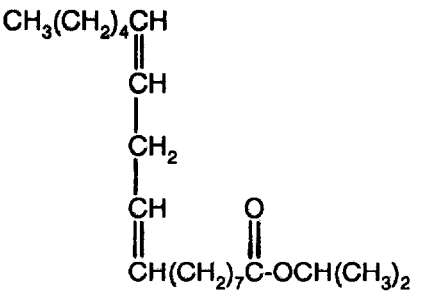
Data available to the Cosmetic Ingredient Review (CIR) concerning the chemistry, use in cosmetic products, acute oral toxicity, and the skin and ocular irritation potential of Isopropyl Linoleate are included in this report. The types of data that are necessary for completion of the safety assessment of Isopropyl Linoleate are listed in the Discussion section.

CHEMISTRY

Chemical and Physical Properties

The commercial product generally known as Isopropyl Linoleate is a mixture consisting of: isopropyl linoleate (64.0–82.0%), isopropyl myristate (0.6% maximum), isopropyl palmitate (2.0–9.0%), isopropyl stearate (3.0% maximum), isopropyl oleate (9.0 to 25.0%), isopropyl linoleate (7.0% maximum), and free linoleic acid (1.75% maximum).[1,2]

The main component isopropyl linoleate is the ester of isopropyl alcohol and linoleic acid that conforms generally to the formula:[3]



The ester is also known as: Linoleic Acid, Isopropyl Ester; 1-Methylethyl-9,12 Octadecadienoate; and 9,12-Otadecadienoic Acid, 1-Methyl Ethyl Ester.

It is a pale yellow, oily liquid consisting of fatty acids derived from a vegetable oil. The results of an ultraviolet (UV) spectral analysis of Isopropyl Linoleate (50 ppm in isopropyl alcohol) did not indicate absorbance in the UVB band (λ max $\approx$ 206 nm).[4] Properties of Isopropyl Linoleate are summarized in Table 1.

Analytical Methods

Isopropyl Linoleate has been analyzed via infrared spectroscopy and gas chromatography.[2,5]

COSMETIC USE

Isopropyl Linoleate is used as a skin conditioning agent-emollient in cosmetics.[6]

The FDA cosmetic product formulation computer printout[7] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[8] 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

Table 1. Properties of Isopropyl Linoleate[1,2]

Form	Pale yellow, oily liquid
Solubility	Soluble in mineral oil and vegetable oil, partly soluble in alcohol, insoluble in water
Specific gravity at 25°C	0.8600 to 0.8700
Refractive index at 25°C	1.453 to 1.454
Acid value	3.5 maximum
Saponification value	163 to 180
Iodine value	120 minimum

assumed ingredient concentration. Isopropyl Linoleate is used in 21 cosmetic products at concentrations ranging from > 0.1% to 10.0% (Table 2).[7]

Isopropyl Linoleate has been approved for use as a cosmetic ingredient in Japan.[9] 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.[10]

TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity of 10.0% Isopropyl Linoleate in corn oil was evaluated using 30 (six groups of 5) male and female fasted, albino rats (weights 200–300 g). The six groups received doses of 2.0, 4.0, 8.0, 16.0, 32.0, and 64.0 cc/kg, respectively, via esophageal catheterization. The following observations were made over a period of two weeks: unkempt coats (8.0 cc/kg); slight diarrhea and unkempt coats (16.0 cc/kg); and wet, oily coats, nasal hemorrhage, and severe diarrhea (32.0 and 64.0 cc/kg). Toxic effects were not observed in animals that received 2.0 and 4.0 cc/kg doses. There were no deaths in any of the groups tested.[11]

Ocular Irritation

The ocular irritation potential of Isopropyl Linoleate (undiluted and 10.0% aqueous suspension) was evaluated in two studies using male New Zealand albino rabbits (six per concentration tested). The test substance was instilled (0.1 ml) into the conjunctival sac of one eye of each animal; the 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:[12] 0 to 110. In both studies, Isopropyl Linoleate was classified as a slight ocular irritant.[13]

In another study, the ocular irritation potential of 10.0% Isopropyl Linoleate in corn oil was evaluated using six albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac; the eyes were not rinsed. Reactions were scored over a period of 7 days (at 1 h, 24 h, etc.) according to the Draize scale: 0 to 110. Ocular irritation was not observed in any of the animals tested.[11]

Skin Irritation

The skin irritation potential of Isopropyl Linoleate (undiluted and 10.0% aqueous suspension) was evaluated using six male New Zealand albino rabbits (2.5–3.5 kg). The

TABLE 2. PRODUCT FORMULATION DATA[7]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			>5–10	*>1–5*	*>0.1–1*
Eye and facial makeup products	1358	9	—	2	7
Face and skin care products, including suntan preparations	1293	7	1	3	3
Miscellaneous hair care products	1027	5	—	3	2
1988 TOTALS		21	1	8	12

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). In the first experiment, 10.0% Isopropyl Linoleate was a nonirritant (Primary Irritation Index = 0.21), and undiluted Isopropyl Linoleate, a slight irritant (Primary Irritation Index = 1.13). In the second experiment, 10.0% Isopropyl Linoleate (Primary Irritation Index = 0.96) and undiluted Isopropyl Linoleate (Primary Irritation Index = 1.00) were classified as slight irritants. The samples tested in the second experiment were purer than those tested in the first experiment.[13]

In another study, the skin irritation potential of 10.0% Isopropyl Linoleate in corn oil was evaluated using six albino rabbits (3 males, 3 females). The test substance (0.5 ml) was applied to abraded and intact dorsal skin that had been clipped free of hair. Each test site was covered with a patch (two layers of light gauze) that was secured with adhesive tape, and the entire trunk was wrapped with a plastic trunk band. The animals were immobilized during the 24 h exposure period. Reactions were scored at the time of patch removal and 72 h later according to the following scales: 1 (very slight erythema) to 4 (severe erythema to slight eschar formation); 1 (very slight edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of exposure). The final score represented an average of the scores recorded at 24 and 72 h. Skin irritation reactions were not observed in any of the animals tested.[11]

Isopropyl Linoleate, undiluted and as 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) 5 days per week for a period of 8 weeks. Excess test substance was wiped from the skin with gauze 30 sec 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 examinations were 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) macroscopic examination must show pathologic reactions 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. In the first experiment, 10.0% Isopropyl Linoleate was relatively well tolerated (IIMM = 1.66) and undiluted Isopropyl Linoleate was very poorly tolerated (IIMM = 3.00; treatment was discontinued after 5 weeks). In the second experiment, 10.0% Isopropyl Linoleate was relatively well tolerated (IIMM = 1.00) and there was a slight intolerance to undiluted Isopropyl Linoleate (IIMM = 2.66). The samples tested in the second experiment were purer than those tested in the first experiment.[5]

SUMMARY

Isopropyl Linoleate is the ester of isopropyl alcohol and linoleic acid. In cosmetics, it is used as a skin conditioning agent-emollient at concentrations ranging from 0.1 to 10.0%.

In an acute oral toxicity study, none of the albino rabbits that received doses of 10.0% Isopropyl Linoleate in corn oil, 2.0 to 64.0 cc/kg, died.

Isopropyl Linoleate (undiluted and 10.0% suspension) was classified as a slight ocular irritant when instilled into the eyes of albino rabbits. Following the instillation of 10.0% Isopropyl Linoleate in corn oil, no ocular irritation reactions were observed in albino rabbits.

In a primary skin irritation study involving New Zealand albino rabbits, undiluted Isopropyl Linoleate and 10.0% Isopropyl Linoleate were classified as a nonirritant and slight irritant, respectively. When the experiment was repeated using purer samples, undiluted Isopropyl Linoleate and 10.0% Isopropyl Linoleate were both classified as slight irritants. In another primary skin irritation study, 10.0% Isopropyl Linoleate in corn oil did not induce reactions in any of the albino rabbits tested.

In albino rabbits, repeated applications of undiluted Isopropyl Linoleate and 10.0% Isopropyl Linoleate were very poorly tolerated and relatively well tolerated, respectively. When the experiment was repeated using purer samples, 10.0% Isopropyl Linoleate was relatively well tolerated and there was a slight intolerance to undiluted Isopropyl Linoleate.

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 CIR Procedures, the Panel informed the public of its decision that the data on Isopropyl Linoleate are insufficient to determine whether this ingredient, under each relevant condition of use, is either safe or unsafe. The Panel released a Notice of Insufficient Data Announcement on April 23, 1990 outlining the data needed to assess the safety of Isopropyl Linoleate. The types of data required include: (1) Human skin irritation and sensitization data and (2) genotoxicity data.

No offer to supply the skin irritation, skin sensitization, or genotoxicity safety test data was received. However, a UV absorption curve indicating no absorbance in the UVB band was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel will issue a Final Safety Evaluation Report—Insufficient Data. When the requested new data are available, the Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Isopropyl Linoleate as used in cosmetic products.

ACKNOWLEDGEMENT

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

REFERENCES

1. ESTRIN, N.F., HAYNES, C.R., and WHELAN, J.M. (1982). *Cosmetic Ingredient Descriptions. CTFA Compendium of Cosmetic Ingredient Composition*. Washington, DC: Cosmetic, Toiletry and Fragrance Association, Inc.

2. ESTRIN, N.F., HAYNES, C.R., and WHELAN, J.M. (1982). *Cosmetic Ingredient Specifications. CTFA Compendium of Cosmetic Ingredient Composition*, Washington, DC: The Cosmetic, Toiletry and Fragrance Association, Inc.
3. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (1982). *Cosmetic Ingredient Dictionary*. Washington, DC: The Cosmetic, Toiletry, and Fragrance Association, Inc., p. 138.
4. VAN DYK CO., INC. (1990). Submission of unpublished data by CTFA. UV spectral analysis on isopropyl linoleate.[1]
5. GUILLOT, J.P., GIAUFFRET, J.Y., MARTINI, M.C., GONNET, J.F., and SOULE, G. (1981). Raw materials used in cosmetology. Informations Chimie **213,** 239–49.
6. NIKITAKIS, J.M. (Editor). (1988). *CFTA Cosmetic Ingredient Handbook*, First Edition. Washington, DC: The Cosmetic, Toiletry and Fragrance Association, Inc., p. 237.
7. FOOD AND DRUG ADMINISTRATION (FDA). (1988). Cosmetic product formulation data on isopropyl linoleate. FDA computer printout.
8. CODE OF FEDERAL REGULATIONS (CFR). (Revised as of April 1, 1984). Title 21 Part 720.4. Voluntary filing of cosmetic product ingredient and cosmetic raw material composition statement. Information requested about cosmetic products. Washington, DC: Government Printing Office.
9. NIKKOL CHEMICALS CO., LTD. (1989). *Cross Reference Index: An Index Cross-referencing the English Names of Cosmetic Ingredients in Japan with CTFA Adopted Names*. Tokyo, Japan: Nikkol Chemicals Co., Ltd.
10. DUPUIS, J. (1989). The European Economic Community (EEC) Cosmetics Directive. Updated Version -incorporating all amendments up to March 15, 1989.
11. BIO-TOXICOLOGY LABORATORIES, INC. (1975). Submission of unpublished data by CTFA. Eye irritation, primary irritation, and acute oral LD_{50} toxicity studies on isopropyl linoleate.[1]
12. DRAIZE, J.H. (1959). Scale for scoring ocular lesions. In; *Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics*. Austin, TX: The Association of Food and Drug Officials of the United States, p. 51.
13. GUILLOT, J.P., GIAUFFRET, J.Y., MARTINI, M.C., GONNET, J.F., and SOULE, G. (1980). Safety evaluation of cosmetic raw materials: results obtained with 160 samples from various origin. pp. 105–108, 109, 110, and 123.

[1]Available for review: Director, Cosmetic Ingredient Review, 1101 17th St., N.W., Suite 310, Washington, DC 20036.