Final Report on the Safety Assessment of Trihydroxystearin[1]

Trihydroxystearin is the triester of glycerin and hydroxystearic acid. It is used as a skin conditioning agent, a solvent, and as a viscosity increasing agent in cosmetic formulations at concentrations up to 5%. In acute oral toxicity studies in rats, no deaths were reported at a dose of 5 g/kg. Trihydroxystearin was reported to be a mild ocular irritant, but not a skin irritant in animal tests. Ames test results indicate that the ingredient is not mutagenic. Clinical testing found no skin irritation. Although the data on Trihydroxystearin are limited, the Cosmetic Ingredient Review (CIR) Expert Panel had previously conducted a safety assessment of Glyderyl Stearate and Hydroxystearic Acid. These data indicate no mutagenic, carcinogenic, or teratogenic effects in animals, and no irritation or sensitization in clinical tests. The data on these two ingredients are considered relevant to the assessment of Trihydroxystearin because of the chemical similarity of the ingredients. The data on Glyceryl Stearate and Hydroxystearic Acid are also consistent with the limited data that are available on Trihydroxystearin itself. Therefore, based on the available animal and clinical data in this report, which includes study summaries from earlier safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate/SE, the Expert Panel concludes that Trihydroxystearin is safe as used in cosmetic formulations.

INTRODUCTION

Trihydroxystearin is the triester of glycerin and hydroxystearic acid that is used as a skin-conditioning agent—occlusive, a solvent, and a viscosity increasing agent—nonaqueous in cosmetics. Although safety test data were not found in the published literature for this ingredient, unpublished data were provided and are described in this report. In addition, the Cosmetic Ingredient Review (CIR) Expert Panel considered that data on Hydroxystearic Acid and Glyceryl Stearate are relevant to the safety assessment of Trihydroxystearin. Hydroxystearic Acid is one of the chemical building blocks of Trihydroxystearin. Glyceryl Stearate is the esterification product of glycerine and stearic acid, making it closely related to Trihydroxystearin. Both Hydroxystearic Acid (Andersen 1999) and Glyceryl Stearate (Elder 1982) were previously reviewed by the Expert Panel and found to be safe as used in cosmetic products. A summary of the findings of each of those reports is provided in the summary section. The Panel relied upon those findings in this safety assessment.

CHEMISTRY

Chemical And Physical Properties

Trihydroxystearin (CAS No. 139-44-6) is the triester of glycerin and hydroxystearic acid that conforms generally to the formula shown in Figure 1 (Wenninger, Canterbery, and McEwen 2000).

Other names for this chemical are as follows: Glyceryl Tri(12-Hydroxystearate; 12-Hydroxyoctadecanoic Acid, 1,2,3-Propanetriyl Ester; Octadecanoic Acid, 12-Hydroxy-, 1,2,3-Propanetriyl Ester; and 1,2,3-Propanetriol Tri(12-Hydroxystearate) (Wenninger, Canterbery, and McEwen 2000); and Glycerol, Tris(12-Hydroxyoctadecanoate); Octadecanoic Acid, 12-Hydroxy-, triester with glycerol; 12-Hydroxystearic Acid Triglyceride; Glycerol 12-Hydroxystearate; Glycerol Tris(12-Hydroxystearate); Glyceryl Tris(12-Hydroxystearate); and Tri-12-Hydroxystearin (Scientific & Technical Information Network International 1996a).

Trihydroxystearin has a formula weight of 939.49 and a melting point of 86°C (Scientific & Technical Information Network International 1996b). Properties of two commercial grades of Trihydroxystearin are summarized in Tables 1 and 2, respectively. The commercial grade noted in Table 2 (Thixcin® E) is another grade of Thixcin® R that has a larger particle size (Rheox, Inc. 1996a).

Methods Of Production

One method of production of Trihydroxystearin involved the hydrogenation of castor oil, in the presence of the reagent nickel, at a temperature of 200°C. Another method of production is the reduction of triricinolein (Scientific & Technical Information Network International 1996b).

Reactivity

Regarding the reactivity of Trihydroxystearin, sources of ignition and strong oxidizers should be avoided (Rheox, Inc. 1995b; 1996b).

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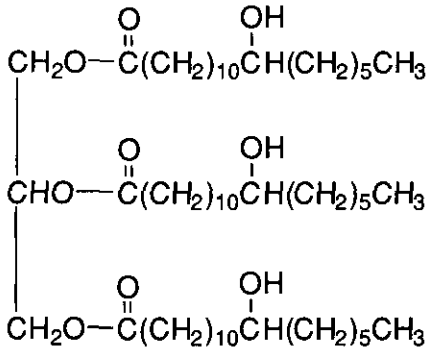

FIGURE 1
Chemical formula for Trihydroxystearin (Wenninger, Canterbery, and McEwen 2000).

USE

Purpose in Cosmetics

Trihydroxystearin has the following functions in cosmetics: Skin-conditioning agent—occlusive; solvent; and viscosity increasing agent—nonaqueous (Wenninger, Canterbery, and McEwen 2000)

Scope and Extent of Use in Cosmetics

United States

The product formulation data submitted to the Food and Drug Administration (FDA) in 1997 indicated that Trihydroxystearin was used in as many as 41 cosmetic product formulations (Table 3) (FDA 1997).

Concentration of use values are no longer reported to FDA by the cosmetics industry (FDA 1992). However, 1984 product formulation data submitted to the FDA indicated that the highest reported use concentration range for Trihydroxystearin was 5% to 10% (FDA 1984). Current concentration of use data indicate that Trihydroxystearin is typically used at concentrations of 0.5% to 5.0% (Rheox, Inc. 1996a).

Cosmetic products containing Trihydroxystearin are applied to the skin, hair, and most parts of the body, and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and have the potential for being applied frequently over a period of several years.

TABLE 1
Properties of Trihydroxystearin—THIXCIN® R (Rheox, Inc. 1995a)

Property	Description
Composition	An organic derivative of castor oil
Form and color	Finely divided white powder
Specific gravity, 250°C/250°C	1.023
Density, 250°C, lb/U.S. gal	8.51
Bulking value, U.S. gal/lb	0.1175
Melting point, °C	86
Fineness, through No. 200 sieve, %	99.8 min
Ash content, %	None
Processing temperature, °F	95–130 (35°–55°C)
Recommended solvent	Aliphatic only

TABLE 2
Properties of Trihydroxystearin—THIXCIN® E (Rheox, Inc. 1994)

Property	Description
Color	White
Form	Finely divided powder
Melting point, °C	85
Density (lbs./U.S. gallon)	8.51
Passing #200 screen, %	100
Ash content	None
Specific Gravity at 25°C	1.023

TABLE 3
Product formulation data on Trihydroxystearin (FDA 1997)

Product category	Total no. of formulations in category	Total no. containing ingredient
Eye shadow	501	1
Eye makeup remover	80	1
Mascara	158	5
Other eye makeup preparations	116	3
Blushers (all types)	229	1
Face powders	245	4
Foundations	283	9
Lipstick	758	6
Makeup bases	125	1
Body and hand skin care preparations (excluding shaving preparations)	776	1
Moisturizing skin care preparations	743	2
Paste masks (mud packs)	247	2
Other skin care preparations	683	3
Suntan gels, creams, and liquids	134	1
Other suntan preparations	43	1
1997 Totals		**41**

International

Trihydroxystearin is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997). This ingredient, which conforms to the specifications of the *Japanese Cosmetic Ingredients Codex*, has precedent for use without restriction in most CLS categories. It is not used in the following four CLS categories: eyeliner, lip, oral, and bath preparations.

Trihydroxystearin also is not included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community 1995).

Noncosmetic Use

Trihydroxystearin has been used as a thickening agent for peanut butter (Elliger, Guadagni, and Dunlap 1972). FDA has listed the following indirect food additive uses in the Code of Federal Regulations (CFR): components of adhesives (21 CFR 175.105), components of resinous and polymeric coatings (21 CFR 175.300), components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), components of paper and paperboard in contact with dry food (21 CFR 176.180), defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.210), cellophane (21 CFR 177.1200), closures with sealing gaskets for food containers (21 CFR 177.1210), polyester resins cross-linked (21 CFR 177.2420), and textiles and textile fibers (21 CFR 177.2800).

Trihydroxystearin is among the inert ingredients that are exempt from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act when used in pesticide formulations that are applied to crops (FDA 1975).

TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity of Trihydroxystearin (Thixcin® R) was evaluated using 10 Wistar-derived, young albino rats (5 males, 5 females; weights = 200–300 g). The animals were fasted prior to administration of a single oral dose (intragastric intubation) of 5 g/kg. The test substance was administered as a 25% corn oil solution. Dosing was followed by a 14-day nontreatment period. The LD_{50} was not achieved at the administered dose of 5 g/kg; no deaths were reported (Food and Drug Research Laboratories, Inc. 1975a). Identical results were reported in another study in which Trihydroxystearin (Thixcin® E, another grade of Thixcin® R) was administered to 10 albino rats (same weights) according to the same procedure (Food and Drug Research Laboratories, Inc. 1975b).

Ocular Irritation

The ocular irritation potential of Trihydroxystearin (Thixcin® R) was evaluated using six young adult, albino rabbits according to the procedure described in 16 CFR 1500.42. The test substance (0.1 ml or 0.1 g) was instilled into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Reactions were scored at 24, 48, and 72 hours and at 7 days postinstillation according to the Draize scale: 0 to 110. Ocular irritation (score = 1) was observed in five rabbits, and all reactions cleared during the 7-day observation period. It was concluded that Trihydroxystearin (Thixcin® R) was a mild, transient ocular irritant (Food and Drug Research Laboratories, Inc. 1975c). Identical results were reported in another study in which Trihydroxystearin (Thixcin® E) was instilled into the conjunctival sac of the eyes of six albino rabbits according to the same experimental procedure (Food and Drug Research Laboratories, Inc. 1975d).

Skin Irritation

The skin irritation potential of Trihydroxystearin (Thixcin® R) was evaluated using six adult albino rabbits. The test substance (0.5 ml or 0.5 g) was applied to shaved and abraded sites, respectively, on the back of each animal. An occlusive patch was applied to each test site for 24 hours; reactions were scored at the time of patch removal. Erythema was observed at intact and abraded sites on one animal, and only at the abraded site in another; edema was not observed. It was concluded that Trihydroxystearin (Thixcin® R) was not irritating to the skin of rabbits (primary irritation index = 0.17) (Food and Drug Research Laboratories, Inc. 1975e). Identical results were reported in another study in which Trihydroxystearin (Thixcin® E) was applied to six albino rabbits according to the same test procedure (Food and Drug Laboratories, Inc. 1975f).

GENOTOXICITY

The mutagenicity of Trihydroxystearin (Thixcin® R) was evaluated in the Ames test (Ames, McCann, and Yamasaki 1975) using the following strains of *Salmonella typhimurium*: TA 1535, TA 1537, TA 1538, TA 98, and TA 100. Two independent mutation tests were conducted. The test substance (suspension in ethanol) was tested at concentrations of 3, 10, 33, 100, 333, and 1000 μg per plate with and without metabolic activation. Control cultures were treated with ethanol and the following substances served as positive controls: 2-Aminoanthracene, sodium azide, 9-aminoacridine, and 2-nitrofluorene. Except for sodium azide (dissolved in sterile, ultrapure water), all positive controls were dissolved in DMSO. 2-Aminoanthracene served as the positive control for metabolically activated cultures, and the remaining chemicals served as positive controls for cultures without metabolic activation. The results noted in the positive-control cultures were within the normal ranges expected for each bacterial strain and activation condition. Vehicle-control values were generally within the normal ranges experienced at the testing facility and reported in the literature for the bacterial strains tested. Thixcin® R was not toxic or mutagenic, with or without metabolic activation, to any of the bacterial strains when tested (in ethanol) to the limit of its solubility over the range

of concentrations tested. Precipitation of the test substance was noted at a concentration of 1000 μg/plate (Inveresk Research International Limited 1995).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

The skin irritation potential of Trihydroxystearin (Thixcin® R) was evaluated using 106 subjects (17 males, 89 females; ages = 11–65). Three subjects did not complete the study (reasons not stated). An occlusive patch containing a small amount of the test substance (volume not stated) was applied either to the inner aspect of the upper arm or to the back of each subject. Patches (secured with occlusive tape) remained in place for 48 hours. Reactions were scored 48 and 72 hours after patch removal according to the Schwartz-Peck scale: 0 (no erythema) to 4+ (erythema and edema with vesiculation and ulceration). Skin irritation was not observed in any of the 103 subjects who completed the study. It was concluded that Trihydroxystearin (Thixcin® R) is not a primary irritant as long as the conditions of contact do not exceed those indicated in this study (Food and Drug Research Laboratories, Inc. 1975g). The results were identical for the same 103 subjects patch-tested with Trihydroxystearin (Thixcin® E) according to the same test procedure (Food and Drug Research Laboratories, Inc. 1975 h).

SUMMARY

Hydroxystearic Acid Report (Andersen 1999)

Hydroxystearic Acid is a fatty acid that is used as a surfactant–cleansing agent in cosmetic products. One method of production involves the catalytic hydrogenation of castor oil.

Product formulation data submitted to FDA in 1996 indicated that Hydroxystearic Acid was used in two cosmetic products categorized as body and hand skin care preparations (excluding shaving preparations).

In male rats fed a diet containing hydrogenated castor oil, Hydroxystearic Acid was deposited in abdominal fat, as well as other body lipids, along with its metabolites (hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid). Hydroxystearic Acid has also been detected in the feces of twelve subjects who presumably ate a normal mixture of foods.

Reduced growth rate was noted in rats fed diets containing 8.7% and 17.3% 12-Hydroxystearic Acid, but not in rats fed 4.3% Hydroxystearic Acid, in a 90-day subchronic oral toxicity study. The results of a second 90-day experiment (no reduction in growth rate) confirmed that the reduction in growth rate previously observed was due to the lower caloric density of diets consisting of 8.7% and 17.3% Hydroxystearic Acid. In both experiments, the results of hematological and microscopic evaluations were unremarkable.

In an in vitro study, Hydroxystearic Acid interfered with oxidative phosphorylation in rat liver mitochondria. Oxidative phosphorylation was uncoupled and mitochondria were damaged.

Hydroxystearic Acid was not mutagenic in strains TA1535, TA100, TA1537, TA1538, and TA98 of *S. typhimurium*. However, Hydroxystearic Acid was classified as mutagenic in strain Hs30 of *Escherichia coli*.

Hydroxystearic Acid was not mutagenic in the L5178Y TK+/− mouse lymphoma assay, with or without metabolic activation; nor did it produce chromosome aberrations in Chinese hamster ovary cells, with or without metabolic activation.

In an 18-month carcinogenicity study (subcutaneous study), Hydroxystearic Acid was classified as tentatively carcinogenic in Swiss-Webster mice. Subcutaneous sarcomas were observed at the site of injection in 9 of the 28 mice (14 per dose group) that were alive at 6 months. All of the sarcomas were observed in the low-dose group (total dose of 4 mg delivered in a total of 8 ml tricaprylin for 80 weeks). The high dose group received a total dose of 80 mg delivered in a total of 8 ml of tricaprylin.

In a second study in which nine A/He male mice received a total intraperitoneal dose of 60 mg Hydroxystearic Acid over a period of 4 weeks, the frequency of lung tumors was within the spontaneous occurrence.

The dermal teratogenicity of two antiperspirant prototype formulations containing 7% Hydroxystearic Acid was evaluated using two groups of 30 Charles River Crl:CD VAF/Plus female rats. There were no test article-related or statistically significant differences in the incidence of fetal malformations or fetal developmental variations between experimental and control groups. Skin irritation reactions, however, were observed in greater than 50% of the dams in both experimental groups. No deaths were reported during the study.

Skin irritation reactions to each of three antiperspirant prototype formulations, each containing 7% Hydroxystearic Acid, were observed in a human primary irritation patch test using 35 volunteers. Semiocclusive patches produced reactions in as many as nine of the subjects, whereas occlusive patches produced reactions in as many as 17 individuals. Only two reactions were noted in the semiocclusive patch controls and only one in the occlusive patch controls. Although the formulations reportedly contained the same concentration of Hydroxystearic Acid, there were small differences in the numbers of individuals reacting to each.

Glyceryl Stearate Report (Elder 1982)

Glyceryl Stearate and Glyceryl Stearate/SE are the esterification products of glycerine and stearic acid. Glyceryl Stearate/SE contains excess stearic acid reacted with potassium hydroxide to produce a self-emulsifying product. Both Glyceryl Stearate and Glyceryl Stearate/SE are white to cream-colored waxlike solids. Either ingredient may contain mono-, di-, and triglyceride impurities and fatty acid impurities.

Glyceryl Stearate and Glyceryl Stearate/SE are widely used in cosmetic formulations as emollients, auxiliary emulsifiers, viscosifiers, stabilizers, bases, and surfactants. Glyceryl Stearate is used in more than 1200 cosmetic formulations at concentrations of ≥0.1% to 50%; Glyceryl Stearate/SE is used in over 200 cosmetic products at concentrations of ≥0.1% to 50%.

Glyceryl Stearate is also widely used in foods as a surfactant, emulsifier, and thickener. Glyceryl Stearate is an antistalant and dough conditioner in breads and is also used in pharmaceutical bases. Glyceryl Stearate has been granted regulatory status as a Generally Recognized as Safe (GRAS) ingredient, an indirect food additive, a direct food additive, and as an over-the-counter (OTC) substance.

In acute oral toxicity studies in rats, Glyceryl Stearate and Glyceryl Stearate/SE at concentrations up to 100% were mildly toxic. In chronic studies, 15% to 25% Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Rats fed a diet containing 25% Glyceryl Stearate for 2 years developed renal calcifications.

Glyceryl Stearate and Glyceryl Stearate/SE at concentrations of up to 100% were mildly irritating or nonirritating to the skin of rabbits. In subchronic and chronic dermal toxicity tests, 4% to 5% Glyceryl Stearate was nontoxic to rabbits but did cause moderate irritation (slight to moderate erythema, edema, atonia, desquamation, and/or fissuring). In seven guinea pig sensitization studies, it was concluded that neither Glyceryl Stearate nor Glyceryl Stearate/SE was capable of inducing sensitization.

In primary eye irritation studies, Glyceryl Stearate and Glyceryl Stearate/SE at concentrations up to 100% were mildly irritating or nonirritating when instilled into the conjunctival sac of the eyes of rabbits.

Glyceryl Stearate, fed to mice in doses of 50 to 100 mg/day or 1.5% in the diet until they died did not induce significant brain or gastric tumor formation, respectively. Five percent Glyceryl Stearate did not promote the carcinogenicity of DMBA in mouse skin.

Results of single and repeated insult patch tests (RIPTs) used to evaluate human skin irritation and sensitization potential of Glyceryl Stearate and Glyceryl Stearate/SE confirmed that both ingredients were nonsensitizing and nonirritating. Glyceryl Stearate was tested at concentrations up to 20% in RIPTs. Products containing 2% Glyceryl Stearate were nonphototoxic and nonphotoallergenic. Worker experience was that Glyceryl Stearate and Glyceryl Stearate/SE are nonirritating to human skin.

Trihydroxystearin

Trihydroxystearin is the triester of glycerin and hydroxystearic acid that is used as a skin-conditioning agent—occlusive, a solvent, and a viscosity increasing agent—nonaqueous in cosmetics. According to one source, the typical use concentration range for this ingredient (marketed as Thixcin® R and Thixcin® E grades that differ only in particle size) in cosmetics is 0.5% to 5.0%. Frequency of use data submitted to FDA in 1997 indicated that Trihydroxystearin has been used in as many as 41 cosmetic products.

In acute oral toxicity studies in which Trihydroxystearin (Thixcin® R and Thixcin® E grades) was tested using albino rats, the LD_{50} was not achieved at a dose of 5 g/kg and no deaths were reported.

Trihydroxystearin (Thixcin® R and Thixcin® E grades tested) was classified as a mild, transient ocular irritant in albino rabbits, but was not irritating to the skin of albino rabbits in 24-hour occlusive patch tests.

Ames test results indicated that Trihydroxystearin (Thixcin® R grade) was not mutagenic to the following *S. typhimurium* strains, with or without metabolic activation, when tested at concentrations ranging from 3 to 1000 μg/plate: TA1535, TA1537, TA1538, TA98, and TA100.

In 48-hour occlusive patch tests, Trihydroxystearin (Thixcin® R and Thixcin® E grades tested) did not induce skin irritation in any of the 103 subjects tested.

DISCUSSION

Although the data on Trihydroxystearin are limited, the CIR Expert Panel had previously conducted a safety assessment of Glyceryl Stearate and Hydroxystearic Acid. These data indicate *no mutagenic, carcinogenic, or teratogenic effects in animals,* and no irritation or sensitization in clinical tests. The data on these two ingredients is considered relevant to the assessment of Trihydroxystearin because of the chemical similarity of the ingredients. The data on Glyceryl Stearate and Hydroxystearic Acid are also consistent with the limited data that are available on Trihydroxystearin itself.

During the open, public comment period on the Tentative Report, a comment was made regarding the absence of sensitization data. The CIR Expert Panel agrees that data on sensitization potential are important in assessing the safety of an ingredient. In this case, there are data on a related ingredient. When tested at concentrations up to 20.0% in human RIPTs involving a large number of subjects, Glyceryl Stearate was neither an irritant nor a sensitizer. Thus, in the absence of sensitization data on Trihydroxystearin, it was concluded that this ingredient is not likely a sensitizer based on data on a chemically similar ingredient. All of the available data suggest that Trihydroxystearin and its component chemical species are safe as used in cosmetic formulations.

CONCLUSION

Based on the available animal and clinical data in this report, *which includes study summaries from CIR Safety* Assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate/SE, the Expert Panel concludes that Trihydroxystearin is safe as used in cosmetic formulations.

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