FINAL REPORT OF THE SAFETY ASSESSMENT FOR WHEAT GERM GLYCERIDES AND WHEAT GLUTEN

The results of tests on laboratory animals and humans for the safety of Wheat Germ Glycerides, Wheat Gluten, and of numerous cosmetic products containing these materials as presently used are reviewed.

These data support the conclusion that Wheat Germ Glycerides (0.25−2%) and Wheat Gluten (1%), in low concentrations in specific product formulations are non-sensitizing and non-irritating to human skin. Limited photopatch testing of Wheat Germ Glycerides in lipstick bases (1−2%) was also negative.

It is concluded that Wheat Germ Glycerides and Wheat Gluten are safe when incorporated in cosmetic products. They constitute no risk to the public as they are presently used in cosmetic products.

CHEMICAL AND PHYSICAL PROPERTIES

Preparation, Composition, and Physical Characteristics

Wheat Germ Glycerides Wheat germ, which is separated from the kernel by conventional milling processes, yields a light yellow or reddish-yellow oil. Transesterification of this wheat germ oil with glycerin forms Wheat Germ Glycerides. This ingredient contains 30 to 40% monoglycerides with di- and tri-glycerides of mixed fatty acids. For use in cosmetic formulations, the glycerides are mixed with 20 to 30% vegetable oils such as safflower oil and corn oil. About 0.05% BHT (butylated hydroxytoluene) and 0.25% di-alpha-tocopherol acetate are added as antioxidants. Details of the chemical composition of Wheat Germ Glycerides is given in Table 1.

TABLE 1. Chemical Composition and Impurities of Wheat Germ Glycerides (CTFA, 1978)[1]

Component Name	Range	Methods by Which Determined
Monoglyceride	30 — 40%	Periodic acid
Diglyceride	—	—
Glycerine	1.5% maximum	Periodic acid
Free fatty acids	0.7% maximum	—
Acid value	1.5 maximum	U.S.P.
Iodine value	110 minimum	Hanus
Acrolein	Negative	Colorimetric

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

Wheat Gluten Wheat Gluten is the proteinaceous, sulfur-rich portion of wheat flour derived from the endosperm of the grain. It is prepared by water washing wheat flour then drying the insoluble matter with careful temperature control. The creamy-tan powder derived from this process is food grade and contains minor amounts of starch and fat (Agatova and Proskuryakov, 1962; CTFA, 1978[1]). Table 2 gives details of its composition.

TABLE 2. Chemical Composition and Impurities of Wheat Gluten (CFTA, 1978)[1]

Test	Range (% W/W)
Protein	75 minimum (moisture-free basis)
Fat	6.5
Moisture	5 — 7.5
Ash	1.0
Carbohydrates	
Starch	13.0
Reducing Sugars	0.5
Crude Fiber	0.5
Other	1.0

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Analytical Methods

The extensive literature on analytical methods applicable to Wheat Germ Glycerides and Wheat Gluten is derived primarily from the milling and food technology industries. These methods include procedures for determining individual components such as fatty acids or their glycerides, amino acids, and carbohydrates (Cah. Tech. Cent. Nat'l. Coord. Etud. Rech. Nutr. Aliment, 1958; Bahl *et al.*, 1976; Benetar and Weneret, 1947; Berliner, 1939; Berliner and Koopman, 1929; Benhamou-Glynn *et al.*, 1965; Chabot, 1925; Cirilli, 1969; Eeckhaut, 1956; Hertwig, 1928; Jones *et al.*, 1963; Lawellin, 1920; Lawrence *et al.*, 1970; Marinelli, 1938; Morison, 1921; Pradac and Prugar, 1961; Röttinger and Woidich, 1928; Röttinger, 1929; Soenen and Pinguair, 1939; Stauffer *et al.*, 1958; Terent'eva *et al.*, 1973).

USES

Wheat Germ Glycerides are used in over 200 cosmetic formulations, most commonly in lipsticks and moisturizers in concentrations ranging from less than 0.1 to 5%. Wheat Gluten is reportedly used in only one category, mascara, at 0.1% or less. The various types of cosmetics and the associated

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concentration levels for Wheat Germ Glycerides and Wheat Gluten are shown in Table 3 (FDA, 1976). The route and frequency of application of cosmetic formulations containing these ingredients can only be inferred, but it is clear that the opportunity exists for eye contact, dermal absorption, and oral ingestion of small amounts. No information is available on possible interactions with other cosmetic ingredients, although Wheat Gluten contains reactive chemical groups such as sulfhydryl and amino groups.

TABLE 3. Product Formulation Data (FDA, 1976)

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product formulations
Wheat Germ Glycerides	Eye shadow	>0.1 to 1	3
	Other eye makeup preparations	>0.1 to 1	3
		≤0.1	1
	Face powders	>0.1 to 1	2
	Foundations	>0.1 to 1	8
		≤0.1	1
	Lipstick	>1 to 5	93
		>0.1 to 1	18
		≤0.1	3
	Makeup bases	>0.1 to 1	5
		≤0.1	1
	Cleansing (cold creams, cleansing lotions, liquids, and pads)	>0.1 to 1	7
		≤0.1	1
	Deodorants (underarm)	>0.1 to 1	1
	Face, body, and hand (excluding shaving preparations)	>1 to 5	1
		>0.1 to 1	11
	Hormone (creams, lotions)	>0.1 to 1	1
	Moisturizing (creams, lotions)	>0.1 to 1	21
		≤0.1	3
	Night (creams, lotions)	>1 to 5	1
		>0.1 to 1	9
		≤0.1	1
	Skin fresheners	≤0.1	1
	Wrinkle smoothing (removers)	≤0.1	1
	Other skin care preparations	>0.1 to 1	15
Wheat Gluten	Mascara	≤0.1	1

BIOLOGICAL PROPERTIES

Animal Toxicity Studies

Acute Studies

Oral Toxicity

Wheat Germ Glycerides In a single oral dose toxicity test of Wheat Germ Glycerides four groups of ten rats each received doses of 8, 16, 32, and 64 g/kg respectively. These doses resulted in one death on the second day after each of the two highest doses. These rats showed congestive changes in many organs and infectious lung conditions, but no effects specifically related to the test material. The surviving animals exhibited no adverse effects, and at the end of the 14-day observation period the average weight gain of those on the two highest doses was greater than that of the rats given the lower doses. From these observations, the LD 50 for Wheat Germ Glycerides would appear to be >64 g/kg (Calogero, 1959)[1].

Another single oral dose test of Wheat Germ Glycerides resulted in one death in ten rats on the 11th day after the lowest dose of 5 g/kg. Three higher doses reaching 14 g/kg, produced no deaths. These rats experienced diarrhea only during the first day at all dose levels. From these data the LD50 for Wheat Germ Glycerides would appear to be >14 g/kg (Calogero, 1977).

Wheat Germ Glycerides in Formulations Twelve formulations of lipstick frosteds, four of lipstick transparents, and four of blushers were each administered orally to groups of five male or five female Sprague-Dawley rats in a single dose of 5 g/kg or 5 ml/kg body weight. These formulations contained Wheat Germ Glycerides in concentrations ranging from 0.25 to 0.5% which are equivalent to doses of 12.5 to 25 ml/kg. No deaths occurred during any of these tests. The animals were observed for 14 days after treatment, but there was neither discussion of adverse symptoms nor any mention of their presence or absence. The procedures described in the Federal Hazardous Substances Act (FHSA) (16 CFR 1500) were followed: acute oral LD50 determinations were made only on test materials that produced deaths at doses of 5 mg/kg or 5 ml/kg (Calogero, 1977).

In a test of lipstick bases containing 1.2 to 2% Wheat Germ Glycerides, an oral dose of 25 g/kg caused no mortality in a group of 100 rats. Irritability and sluggishness immediately after dosing were attributed to the large volume of material administered. The animals were sacrificed and autopsied after 14 days. No gross abnormalities were reported (CTFA, 1976)[1].

Three skin treatment products containing 0.1% Wheat Germ Glycerides were each administered in single oral doses to rats and were reported to have LD50 values of >5 g/kg, >10 g/kg, and >10 g/kg, respectively (Calogero, 1976)[1].

Wheat Gluten A mascara base containing 1% Wheat Gluten was administered by gavage to 30 rats in a single dose of 25 mg/kg and to 40 rats in a

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dose of 50 g/kg. Two deaths at the lower dose and one at the higher dose occurred within 48 hours. The survivors generally showed irritability, diarrhea, and ataxia during the first 24 hours, with complete recovery in one week. After 14 days, autopsy findings in survivors were negative. The dead animals showed intestinal bloating or obstruction, probably due to the large volume of test material administered (CTFA, 1976)[1].

Eye Irritation

Wheat Germ Glycerides Two drops of undiluted Wheat Germ Glycerides in a rabbit eye produced minimal irritation of the conjunctiva in four of ten rabbits (the score 0.5 of a possible maximum of 110) when tested by the Draize method. This effect was observed in the first two days after a single application and disappeared on the third day. The highest average score was 0.3 (Kolmar Research Center, 1959).

In another study involving six rabbits, 0.1 ml of Wheat Germ Glycerides in the eye of six rabbits (Draize method) produced no irritation (Calogero, 1977)[1].

Wheat Germ Glycerides in Formulations Numerous formulations each of lipstick creams, frosteds, and transparents, and of blushers were tested for eye and mucosal surface irritation potential in groups of six rabbits each. The concentrations of Wheat Germ Glycerides in these products ranged from 0.25 to 0.50%. Evaluation of the effects on the cornea, iris, and conjunctiva, and of chemosis and discharge was done by the method of scoring for ocular lesions as described by Draize (1965). Four of the 12 lipstick creams and one of the four blushers showed low irritation indices. Two of the 12 lipstick creams tested scored 2 out of a possible score of 110. Of the 28 products studied, all others were scored zero (Calogero, 1977)[1].

In similar tests of a lipstick base at concentrations of 1.25 and 2.0% of Wheat Germ Glycerides on groups of 24 and 30 rabbits, respectively, no positive reactions were observed in any of the ocular parameters scored (CTFA, 1976)[1].

Three products containing 0.1% Wheat Germ Glycerides in a primary eye irritation test on rabbits produced transient minimal irritation of the conjunctiva in two cases and no irritation in the third (Calogero, 1975)[1].

Wheat Gluten A mascara base containing 1% Wheat Gluten was tested for eye irritation in rabbits by both the Draize procedure and the procedures required under FHSA. A mild circumcorneal injection was noted in 50% of the animals and a mild discharge in two animals. These changes were thought to be typical of those resulting from foreign objects in the eye and were attributed to drying of the mascara base. Complete recovery occurred within 72 hours (CTFA, 1976)[1].

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Skin Irritation

Wheat Germ Glycerides Different lots of Wheat Germ Glycerides were tested in rabbits for acute dermal toxicity by the Draize method and for primary dermal irritation using the procedures required under the Consumer Product Safety Act, 16 CFR 1500.3 (c) (4) and 1500.41. A mild irritation was observed especially on the abraded skin, but there was no evidence of systemic toxicity as reflected by food consumption or body weight. It was concluded that Wheat Germ Glycerides is not a primary irritant (Calogero, 1959, 1975, 1977)[1].

Other studies of cosmetic products containing Wheat Germ Glycerides, such as several lipstick preparations, liquid makeup, and others, revealed minimal skin irritation in a few of the test rabbits (Calogero, 1976; CTFA, 1976; Calogero, 1965)[1].

Guinea Pig Sensitization Sensitization by Wheat Germ Glycerides was evaluated in two groups of six guinea pigs each. One group received olive oil and the other a 0.1% solution of Wheat Germ Glycerides in olive oil. Initial injections were 0.05 ml intracutaneously. Subsequent injections of 0.1 ml were similarly given three times a week for a total of ten injections. Two weeks later a challenge injection of 0.05 ml was made. Observations were made on the days following the first and last injection. Mild reactions were observed in all animals except there was no reaction in one each of the control and experimental groups. Average scores for the experimental group were slightly less than for the controls indicating that Wheat Germ Glycerides is not a skin sensitizer in the guinea pig (Calogero, 1959)[1].

Subchronic Studies

Wheat Germ Glycerides A twelve-week feeding study was conducted on Wheat Germ Glycerides using weanling rats in three groups of five males and five females. They were given a basal diet supplemented with 1, 5 or 25% Wheat Germ Glycerides. An equal number of rats placed on the same basal diet (Rockland Rat Diet) served as controls. Two rats died: one male at four weeks in the control group and one female at 10 weeks in the 5% glycerides group. The results of observations on weight gain, efficiency of food utilization, hemoglobin, white and red blood cell counts, and liver and kidney weights as percents of body weights, all failed to show any evidence of adverse effects induced by the material under investigation. Numerous gross and histopathologic changes were found at the end of the feeding period but none of these was dose-related. The same lesions appeared in the controls and at the same rate of incidence as in the test animals. These data are tabulated in Table 4.

Wheat Gluten In 1944 it was observed that Wheat Gluten flour at a level of 10% or higher in the diet produced "running fits" in dogs (canine hysteria) as early as three days after the start of the diet (Wagner and Elvehjem, 1944). This condition was subsequently shown to be due to a toxic factor produced by the interaction of the Wheat Gluten with the nitrogen trichloride used in the

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TABLE 4 Rat Subchronic Feeding of Wheat Germ Glycerides (Calogero, 1959)[1]

Dietary Level	Number & Sex	12-Week Survivors	Weight Gain	Feed Efficiency gm/100 gm	Hemoglobin gm/100 ml	RBC $X10^{-6}$	WBC $X10^{-3}$	M/F Liver % Body Wt	M/F Kidney % Body Wt
None	5 M	4	205.2	11.2	14.8	6.5	21.5	3.9—5.9	1.1—2.6
	5F	5	154.3	6.2	14.0	6.0	12.2		
1%	5M	5	184.8	10.5	14.0	5.8	21.7	4.5—6.8	1.0—2.1
	5F	5	107.3	5.9	14.0	6.3	17.5		
5%	5M	5	172.1	10.2	12.8	6.0	18.2	3.9—5.6	1.3—2.1
	5F	4	139.3	6.6	12.8	5.6	13.4		
25%	5M	5	166.4	9.5	14.8	6.4	19.2	4.7—5.8	0.9—1.3
	5F	5	148.1	8.7	15.5	6.2	20.5		

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commercial processing of the flour (Erickson, *et al.*, 1947). This treatment of flour is no longer practiced. In a study by Newell *et al.*, (1949), it was shown that high levels of Wheat Gluten itself in the diet are tolerated by several species of animals, including human subjects.

CLINICAL ASSESSMENT OF SAFETY

Dermatologic Studies

Wheat Germ Glycerides Modified Draize-Shelanski repeated insult patch tests using 2% Wheat Germ Glycerides in a lipstick base were performed on 1154 subjects. Eight positive reactions occurred. These were mild and transitory and interpreted as non-specific irritant reactions by the investigating dermatologists who concluded that the product and/or ingredients caused no significant irritation (CTFA, 1977)[1].

Modified Draize-Shelanski repeated insult patch tests were performed on 200 subjects using three product formulations, each containing less than 0.1% Wheat Germ Glycerides. Test results indicated that the materials were considered to be non-irritating and non-sensitizing (Calogero, 1975)[1].

In another study using 0.25—0.5% Wheat Germ Glycerides in lipstick creams, lipstick frosteds, lipstick transparents, and blushers, the Modified Draize-Shelanski repeated insult patch test was performed on 150 subjects. No positive reactions occurred with lipstick creams, lipstick frosteds and blushers. There was one positive patch test (out of 150) with lipstick transparents. The investigators concluded that these products are non-irritating and non-sensitizing (Calogero, 1977)[1].

Schneider (1955)[1] tested patients with Wheat Germ Glycerides and concluded that 2% was non-irritating on healthy skin. Details of this study are lacking.

Five photopatch tests on 139 subjects using 2% Wheat Germ Glycerides in a lipstick base were performed and no significant reactions occurred. Photopatch testing of 24 subjects using 1% Wheat Germ Glycerides in lipstick caused no irritant or hypersensitivity reactions (CTFA, 1978, 1977)[1].

An in-use test of 149 subjects using 2% Wheat Germ Glycerides in a lipstick base under normal usage conditions resulted in no "untoward reactions" (CTFA, 1977)[1].

Wheat Gluten The Shelanski repeated insult patch test technique was used to test two mascara base products each containing 1% Wheat Gluten. Fifty subjects were employed and no adverse reactions occurred (CTFA, 1977)[1].

The modified Draize-Shelanski patch test was performed on 202 subjects using 1% Wheat Gluten in a mascara base. Eleven reactions occurred: two were considered to be due to preservatives and nine were considered "non-specific irritation" without further explanation (CTFA, 1977)[1].

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One percent Wheat Gluten in a mascara base was worn by subjects in normal usage under the supervision of a dermatologist. No objective signs of dermatitis were noted but the duration of the study was not reported (CTFA, 1977)[1].

Two products containing Wheat Gluten in use for five years were studied. The number of reactions per 100,000 sold was 2.0 for one product and 0.15 for the other product. None of the reactions was attributed to Wheat Gluten (CTFA, no date).

Dermatitis Herpetiformis is a chronic papular-vesicular eruption affecting all extensor surfaces. It is occasionally associated with small bowel disease resembling gluten-sensitive enteropathy, sometimes termed celiac disease or non-tropical sprue (Katz and Strober, 1978; Fry *et al.*, 1973; Marks and Whittle, 1969; Seah *et al.*, 1972).

The pathogenesis of Dermatitis Herpetiformis is not certain. An immunologic component is suggested by the finding of immunoglobulin A deposits in the dermal papillae in most patients (Katz and Strober, 1978; Van Der Meer, 1969; Seah *et al.*, 1973; Marks and Shuster, 1970). Eterman *et al.* (1977) examined these deposits but found no antibodies to wheat. However, Huff *et al.* (1979) have demonstrated circulating antibodies to wheat protein in Dermatitis Herpetiformis. Massey *et al.* (1977) have suggested that gluten entering the serum from a damaged intestinal mucosa forms an immune complex which activates complement in the skin via the alternate pathway thus causing an inflammatory reaction.

Since the concentration of gluten in cosmetics is low ($\leq 0.1\%$), there is no likelihood that enough Wheat Gluten could be absorbed by the percutaneous route or by inadvertent ingestion from cosmetic products to precipitate a flare-up of either gastrointestinal or cutaneous symptoms.

SUMMARY

The results of tests on laboratory animals and humans for the safety of Wheat Germ Glycerides, Wheat Gluten, and of numerous cosmetic products containing these materials attest to the safety of these wheat products as presently used.

There are data supporting the conclusion that Wheat Germ Glycerides (0.25—2%) and Wheat Gluten (1%), in low concentrations in specific product formulations are non-sensitizing and non-irritating to human skin. Limited photopatch testing of Wheat Germ Glycerides in lipstick bases (1—2%) was also negative. Data from provocative or maximization testing of these individual materials in a wide range of concentrations are, however, lacking in human beings.

In tests on rats given single oral doses of these ingredients and of a limited number of their formulations, no LD50 values could be obtained because of the excessively large doses required. This illustrates the absence of significant acute systemic toxicity in these ingredients and their formulations and indi-

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cates a wide margin of safety should accidental oral ingestion occur. Subchronic feeding studies of high levels of Wheat Germ Glycerides and of Wheat Gluten in several species including human beings, provided further evidence that there is no risk from the use of these materials as cosmetic ingredients.

Numerous tests for eye and skin irritation in rabbits and skin tests in humans have shown only occasional minimal and rapidly reversible effects. No evidence of sensitization was observed in tests with the glycerides or the gluten.

The safety assessment of these ingredients rests on the information at hand and on the considerable usage in various concentrations in a variety of cosmetic formulations. Additional biological evaluation of these ingredients might reasonably be expected to incorporate more extended studies on the following:

1. Provocative or maximization patch testing on humans over a wide range of concentrations of both ingredients with observations for irritation, sensitization, photoirritation, and photosensitization.
2. Extension of the existing tests of both ingredients for dermal effects (as in 1 above) in humans at concentrations beyond the present data, for which the highest is 2%, to above 5% which is the maximum concentration reported in formulations.

CONCLUSIONS

On the basis of the information available, which the Expert Panel believes to be relevant and accumulated in a reasonable manner, the Panel concludes that Wheat Germ Glycerides and Wheat Gluten are safe when incorporated in cosmetic products and constitute no risk to the public in its present cosmetic use of these products.

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