Final Report on the Safety Assessment of PEG-2, -3, -5, -10, -15, and -20 Cocamine[1]

The PEGs Cocamine are the polyethylene glycol ethers of the primary aliphatic amine derived from coconut oil. These ingredients are used in cosmetic formulations as surfactants which function as emulsifying and solubilizing agents. Very little data were available on metabolism and toxicity, and no clinical data were found or provided. Toxicity data, including reproductive and developmental toxicity, carcinogenesis data, and clinical testing data available from previous safety assessments on Polyethylene Glycol and Coconut Oil were summarized. The principal finding related to PEGs was based on clinical data in burn patients; PEGs were mild irritant/sensitizers and there was evidence of nephrotoxicity. No such effects were seen in animal studies on intact skin. Cosmetic manufacturers should adjust product formulations containing Polyethylene Glycol to minimize any untoward effects when products are used on damaged skin. Various PEGs Cocamine were found to be mild to moderate skin irritants and were ocular irritants. PEG-15 Cocamine was negative in bacterial mutagenicity studies. Although metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, it was considered unlikely that the relevant metabolites would be found in or produced from the use of PEGs Cocamine in cosmetic formulations. Of concern was the possible presence of 1,4-dioxane and ethylene oxide impurities. The importance of using the necessary purification procedures to remove these impurities was stressed. The limited data on PEGs Cocamine and the related data on other ingredients, however, were not sufficient to support the safety of PEGs Cocamine for use in cosmetic formulations. Additional data needs include: (1) physical and chemical properties, including impurities, and especially nitrosamines; (2) genotoxicity in a mammalian system; if the results are positive, then a dermal carcinogenesis study using National Toxicology Program (NTP) methods may be needed; (3) 28-day dermal toxicity using PEG-2 Cocamine; and (4) dermal sensitization data on PEG-2 Cocamine.

INTRODUCTION

The following report is a review of the safety data on PEG-2, -3, -5, -10, -15, and -20 Cocamine. These cosmetic ingredients are surfactants used as emulsifying and solubilizing agents. Chemically, these ingredients are the polyethylene glycol (PEG) ethers of the primary aliphatic amine derived from coconut oil. Note that the different chain length PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide used corresponding to the number in the name.

These two basic components have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and Final Reports have been published. The following conclusions were made:

> PEG-6, -8, -32, -75, 150, -14M, and -20M are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).
>
> Coconut Oil, and its derivatives, Coconut Acid, Hydrogenated Coconut Oil, Hydrogenated Coconut Acid are safe for use as cosmetic ingredients (Elder 1986).

The relevant data from the Final Safety Assessments of the PEGs and Coconut Oil and its derivatives have been summarized in this review as a further basis for the assessment of safety of PEG-2-20 Cocamine.

CHEMISTRY

Definition and Structure

PEG-2, -3, -5, -10, -15, and -20 (CAS No. 61791-14-8 [generic]) Cocamine are the polyethylene glycol ethers of the primary aliphatic amine derived from Coconut Oil. These ingredients conform to the formula shown in Figure 1, where R represents the alkyl groups derived from Coconut Oil and x + y has an average value equal to the number in the name (see Method of Manufacture) (Wenninger and McEwen 1997). Other names for these compounds include Polyethylene Glycol (x + y) Coconut Amine, Polyoxyethylene (x + y) Coconut Amine (Wenninger and McEwen 1997), and Polyoxyethylene (POE) Cocamine (Newburger, Jones, and Kottemann 1995).

Physical and Chemical Properties

PEG-15 Cocamine is a clear, light brown, oily liquid. It is soluble in water, isopropyl alcohol, and benzene. The specific gravity ranges from 1.040 to 1.046. Allowable moisture and ash are 3% and 0.5% maximum, respectively (Nikitakis and McEwen 1990).

The properties of the different chain length PEGs vary as a function of molecular weight, with PEG-32 being a solid and PEG-8 being a viscous liquid (Andersen 1993). Coconut Oil is a pale yellow, semisolid, edible oil that is stable in air at room temperature. It is miscible in carbon disulfide, chloroform, ether, and petroleum benzin. Coconut Oil and Coconut Acid are both

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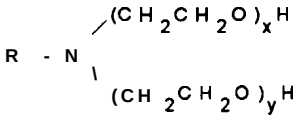

FIGURE 1
Chemical formula for PEGs Cocamine polymers (Wenninger and McEwen 1997). R represents the alkyl groups derived from Coconut Oil and x + y has an average value equal to the number in the name.

soluble in mineral oil and isopropyl myristate, but are alcohol and water insoluble. Due to its high degree of saturation, Coconut Oil is resistant to atmospheric oxidation at room temperature (Elder 1986).

Method of Manufacture

The PEG-n Cocamine polymers are manufactured by condensing Coconut Acid with the ingredient's corresponding number of moles (n) of ethylene (Hunting 1983).

PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide polymerized indicated by the number in the name (Andersen 1993).

Coconut Acid is a mixture of fatty acids derived from Coconut Oil. Coconut Oil is obtained by expression from the kernels of the seeds of *Cocos nucifera.* The primary constituents of Coconut Oil are trimyristin, trilaurin, tripalmitin, tristearin, and various other triglycerides. About 90% of the oil is saturated. The expressed material has a water content of 4–10%. The fatty material is isolated after hydrolysis of Coconut Oil and then distilled to form Coconut Acid (Elder 1986).

Analytical Methods

Newburger, Jones, and Kottemann (1995) determined PEG-1.5 Cocamine in cosmetic formulations containing polyethylene glycols and/or propylene glycols using partition chromatography on Celite and infrared spectrometry.

Impurities

Silverstein et al. (1984) reported that PEG-6 may contain small amounts of monomer and dimers. The amounts were not quantified. Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger, Azaz, and Donbrow 1975). The amount of peroxide in PEG is dependent upon the molecular weight of the PEG and its age. The older the compound, the greater the concentration of peroxides. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEG, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity, Hill, and La Via 1975).

Ethoxylated surfactants may also contain 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974; Hoch-Ligeti, Argus, and Arcos 1970; Argus, Arcos, and Hoch-Ligeti 1965). In the CIR safety assessment of the PEGs Stearate, the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations (Elder 1983).

Coconut Oil is usually low in color bodies, pigments, phosphatides, gums, and other nonglyceride substances commonly found in larger quantities in other vegetable oils. It may contain free fatty acids, low concentrations of sterols, tocopherol, and squalene. The characteristic coconut flavor is due to the presence of approximately 150 ppm lactones that are present as a series of *d*-lactones with 6, 8, 10, 12, and 14 carbon atoms. Crude samples of Coconut Oil contain traces of polycyclic aromatic hydrocarbons, particularly when the copra is smoke-dried. A combination of activated charcoal treatment and steam vacuum deodorization are the common refining methods most likely to remove the hydrocarbons from the edible oils. Aflatoxin contamination of raw and dried copra have been reported. Improper drying, handling, and storage greatly increase the possibility of contamination by aflatoxins, secondary metabolites of the mold *Aspergillus flavus*, which grows on copra. Smoke drying of copra inhibited aflatoxin formation (Elder 1986).

USE

Cosmetic

The PEGs Cocamine are surfactants used as emulsifying and solubilizing agents (Wenninger and McEwen 1997). The product formulation data submitted to the Food and Drug Administration (FDA) in 1996 indicated that only PEG-2, -3, -15, and -20 Cocamine are in use, and that they are collectively used in 95 cosmetic formulations (Table 1) (FDA 1996). Concentration of use data submitted by Cosmetic, Toiletry, and Fragrance Association (CTFA) in 1995 reported generically that PEGs Cocamine were used in hair bleach and hair color at concentrations of 20% and 8%, respectively (CTFA 1995a), and that specifically, PEG- 15 Cocamine was used at concentrations up to 1.3% in various products (CTFA 1995b) as shown in Table 2.

International

PEG-2 Cocamine is listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) and must conform to

TABLE 1
Cosmetic product formulation data (FDA 1996)

Product category	Total no. formulations in category	Total no. of formulations containing ingredient
PEG-2 Cocamine		
Hair dyes and colors	1612	5
Hair tints	57	10
1996 total		**15**
PEG-3 Cocamine		
Hair dyes and colors	1612	14
1996 total		**14**
PEG-15 Cocamine		
Colognes and toilet waters	834	2
Powders	307	1
Other fragrance preparations	195	1
Tonics, dressings, and other hair grooming aids	604	6
Other personal cleanliness products	339	2
Aftershave lotion	268	1
Cleansing preparations	820	3
Body and hand preparations (excluding shaving)	1012	2
Moisturizing preparations	942	4
Skin fresheners	244	3
1996 total		28
PEG-20 Cocamine		
Bubble baths	211	1
Hair conditioners	715	2
Hair dyes and colors	1612	34
Hair lighteners with color	9	1
1996 total		38

the standards of the *Japanese Cosmetic Ingredient Codex* (JCIC) (Yakuji Nippo, Ltd. 1994). It can be used in all CLS categories except eyeliners, lipsticks and lip creams, and dentifrices without restriction.

TABLE 2
Concentration of use of PEGs Cocamide polymers in cosmetic formulations (CTFA 1995a,b)

Formulation	Concentration (%)
PEGs Cocamine	
Hair bleach	20
Hair color	8
PEG-15 Cocamine	
Shower gel	1.0
Eyeshadow	1.3
Fragranced body freshener	1.0
Shampoo	0.8
Hair dressing	0.8
Hair fixative	< 1

BIOLOGICAL PROPERTIES

Absorption, Metabolism, Distribution, and Excretion

Gastrointestinal absorption of PEG is dependent on the molecular weight of the compound. In general, the larger the molecular weight of the PEG compound, the lesser absorption that occurs. In both oral and intravenous studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human bum patients. monomeric ethylene glycol was isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

Results of clinical dietary studies suggest that 95–98% of ingested Coconut Oil is absorbed. When Coconut Oil was used as a saturated fat control for metabolism studies with rats, it caused slight increases in serum cholesterol concentrations. Longevity was not affected by diets containing Coconut Oil. In another study using rats, 60% of a 6 g/kg dose Coconut Oil adminstered by intubation was absorbed within 6 h (Elder 1986).

ANIMAL TOXICOLOGY

Acute Toxicity

The oral LD50 of PEG-2 Cocamine was approximately 1.3 g/kg for rats (CTFA 1978a). In similar studies, the LD50 was 0.75 g/kg (Goater et al. 1970) and 1 g/kg for PEG-2 Cocamine (CTFA 1978b), and 1.2 g/kg for PEG-15 Cocamine (CTFA 1978c).

The acute oral LD50 in rabbits of 100% PEG-6 was 17.3 g/kg; that of 100% PEG-75 was 76 g/kg. Acute dermal toxicity studies did not result in mortality after rabbits were given 20 ml/kg doses of undiluted PEG-6 or 40% PEG-20M (Andersen 1993).

No deaths occurred after undiluted Coconut Oil and Hydrogenated Coconut Oil were administered to rats via intubation in 5 g/kg doses. Undiluted Hydrogenated Coconut Oil did not cause mortality after a single 3 g/kg dermal application in guinea pigs (Elder 1986).

Short-Term Toxicity

The minimum lethal daily dose of PEG-5 Cocamine administered to guinea pigs for 8 days was 500 mg/kg (Goater et al. 1970).

Schafer and Bowles (1985) fed 2.0% ethoxylated Cocamine (the number of moles of ethylene oxide polymerized was not specified) treated feed to deer mice for 3 days. The LD50 was > 1200 mg/kg/day.

There was no evidence of toxicity in rabbits that received daily dermal applications of PEG-20M (0.8 g/kg/day) for 30 days; however, transient, mild erythema was observed. The only evidence of systemic toxicity that resulted from dermal exposure was renal failure in rabbits that received repeated applications of an antimicrobial cream containing 63% PEG-6, 5% PEG-20, and 32% PEG-75 to *excised skin* for 7 days (Andersen 1993).

Subchronic Toxicity

Fifty female, albino Charles River CHR-CD rats were placed into five groups of 10 rats each. The rats were housed individually in temperature-controlled cages. Feed and water were provided ad libitum. After a 2-week acclimation period, the rats received the test materials to their shaved skin by gentle inunction. Group 1, the control group, received 2.0 ml/kg mineral oil once daily, 5 days a week, for 6 weeks. The same dose of 10% PEG-15 Cocamine was applied 30 times to group 2 rats. The other three groups received different test materials (not listed). Observations for general appearance, behavior, pharmacologic and/or toxicologic signs were recorded daily. Initial and weekly body weights were measured, as well as at necropsy. At the end of the study, the rats were fasted for 16 hours overnight. Blood samples were drawn by orbital sinus puncture while the rats were under ether anesthesia. Hematocrit, hemoglobin concentration, erythrocyte count, white blood cell count (both total and differential), blood urea nitrogen concentration, multiple cell volume, serum alkaline phosphatase activity, serum glutamic oxaloacetic transaminase activity, serum glutamic pyruvic transaminase. and fasting blood glucose were all determined. All rats survived for the length of the study. No adverse effects were observed in weight gain, physical appearance, or behavioral signs. Application sites of treated skin did not significantly differ from untreated controls. A few rats in each group scratched the application sites, probably due to caking of the test material or by the nicking of the skin while shaving. No evidence was found that the scratching could be attributed to the application of the chemicals. All rats were killed by ether overdose for necropsy. The brain, liver, kidneys, spleen, adrenal glands, lungs, heart, and uterus were then weighed and portions of each preserved. Portions of the intestines, pancreas, skin, and stomach were also fixed. Slides of kidneys, bile duct, liver, spleen, and skin were examined microscopically, as were slides of bone marrow. Mean neutrophil and lymphocyte values of PEG- 15 Cocamine-treated rats were significantly higher or lower than controls, but fell within the historical range of the laboratory rats, and were not accompanied by other changes. Therefore, researchers concluded that the differences were not related to the treatment. At necropsy, no changes were observed that could be attributed to the test material, and no significant changes in relative or absolute organ weights were observed. At microscopic examination, no lesions were found that were related to the application of PEG-15 Cocamine. Researchers concluded that no systemic toxic effects occurred in the tested rats at the applied dosage (CTFA 1978h).

In 90-day oral toxicity studies involving groups of albino rats, the highest and lowest molecular weight PEGs tested (PEG-20M and PEG-6, respectively) did not induce toxicity or death when administered daily in the diet (PEG-20M) or in drinking water (PEG-6) at concentrations of 4% or less (Andersen 1993).

In a subchronic study using rats, 25% Coconut Oil in feed was administered. A 20–30% higher progressive increase in liver fat content was observed, compared to controls. Fatty acid change of the liver was slight and no other pathological changes were observed (Elder 1986).

Chronic Toxicity

Toxic effects were not observed in dogs that received 2% PEG-8, PEG-32, or PEG-75 in the diet for 1 year (Andersen 1993).

Supplementation of the lifetime diet of mice with 15% Hydrogenated Coconut Oil did not adversely affect the lifespans of mice (Elder 1986).

Ocular Irritation

The right conjunctival sac of six New Zealand white rabbits was instilled with 0.10 ml PEG-2 Cocamine, and observations were made after 24, 48, and 72 hours, and after 7 days. The irritation scores (out of a maximum possible score of 110) were: 63.7 at 24 hours, 62.7 after 48 hours, 61.3 after 72 hours, and 64.5 after 7 days. This ingredient was classified as an ocular irritant (CTFA 1978a).

In another study with six rabbits, the average ocular irritation scores for PEG-2 Cocamine were 27.0 at 24 hours, 36.2 at 48 hours, and 39.3 at 72 hours. The investigators noted that the average score increased between 24 and 72 hours, which seemed to be due to a mild, but persistent, involvement of a large area of the cornea (CTFA 1978f).

Goater et al. (1970) reported that 10% aqueous PEG-5 Cocamine caused moderate, but transient, inflammation or reddening of the eyes of rabbits.

A study of PEG-l 5 Cocamine (as supplied) was conducted in a similar fashion. Following instillation of this ingredient into the conjunctival sac of six rabbits, cornea1 opacity and conjunctival inflammation, swelling, and ocular discharge were observed in all of the rabbits at all three time periods. A decreased iridic response to light was observed in five rabbits at the 48-hour interval, and the remaining rabbit developed this condition at 72 hours. The irises of two rabbits had no reaction to light at 72 hours (CTFA 1978g).

Ocular irritation scores were obtained using test methodology prescribed in the *Code of Federal Regulations* (CFR Title 16 Parts 1500.3, 1500.40, 1500.41, and 1500.42. Testing methods). Scores for PEG- 15 Cocamine were 32.33, 39.83, and 42.0 at 24, 48, and 72 hours, respectively, out of a maximum possible score of 110. Corneal irritation was involved at all readings (Protameen Chemicals, Inc. 1995).

PEGs -6 and -75 did not cause cornea1 injuries when instilled (undiluted, 0.5 ml) into the conjunctival sac of rabbits. PEG-8 (35% solution, 0.1 ml) and PEG-32 (melted in water bath, 0.1 ml) induced mild ocular irritation in rabbits (Andersen 1993). The results of several studies indicate that the ocular irritation potential of undiluted Coconut Oil is low (Elder 1986).

Dermal Irritation and Sensitization

Six New Zealand white rabbits were treated topically with 0.5 ml PEG-2 Cocamine on both abraded and intact sites on their back and flanks. Applications were covered with gauze patches and taped to the skin. Irritation scores were determined at 24 and 72 hours following application. Irritation was observed on all the rabbits. The primary skin irritation index (PII) was 3.9 out of a maximum of 8 (CTFA 1978a).

In similar studies, the PIIs for PEG-2 and PEG- 15 Cocamine were 2.4 and 1.4, respectively. The irritation score of PEG-2 Cocamine was due to severe erythema, which was observed at 72 hours. Erythema was also observed with PEG- 15 Cocamine. However, no edema was observed with either ingredient. PEG-2 Cocamine was classified as a moderate irritant, and PEG-15 Cocamine was considered a mild irritant (CTFA 1978d,e).

In another study, semiocclusive patches of 0.5 ml PEG-2 Cocamine (concentration not stated) were applied to the intact skin of six New Zealand white rabbits. The patches were kept in contact with the skin for 4 hours, after which the skin was rinsed. Examinations of the skin were made at the time of patch removal and at 24 and 48 hours later. The PIIs for time intervals were 6.2 at 4 hours, 7.2 at 24 hours, and 7.3 at 48 hours. Subcutaneous hemorrhaging and blanching were observed in all of the animals at 24 hours and in one rabbit at 48 hours. Eschar and necrotic areas were observed at both the 24 and 48 hours readings. The investigators concluded that PEG-2 Cocamine was corrosive to the skin (Hazelton Laboratories America, Inc. 1985).

The PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. In skin irritation tests, undiluted PEG-6 was applied to the skin of rabbits for 4 hours and 50% PEG-75 was applied to guinea pigs for 4 days and to rabbits over a 13-week period. In the guinea pig skin sensitization test, PEG-75 was tested at a concentration of 0.1% (Andersen 1993).

Undiluted Coconut Oil did not cause skin irritation in rabbits during a 24-hour single-insult occlusive patch test. It was also nonsensitizing in a Magnusson-Kligman Maximization test. No irritation was observed when bar soaps containing 13% Coconut Oil were evaluated in single-insult occlusive patch tests using rabbits with abraded and intact skin. The primary irritation threshold of Hydrogenated Coconut Oil was 5% in ethyl alcohol, which produced slight irritation to guinea pigs upon repeated application. This concentration was nonsensitizing in a test using a modified Buehler technique (Elder 1986).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylene Glycol and Its Ethers

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers (e.g., methoxyethanol, a.k.a. ethylene glycol monomethyl ether) are reproductive and developmental toxins. The CIR Expert Panel undertook a separate, limited scope review of these compounds in order to assess the possibility that PEG-derived cosmetic ingredients could present similar concerns (CIR 1996). In summary, this report concluded that the ethylene glycol monoalkyl ethers are not themselves toxic, but rather, that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, the report also concluded that the toxicity of the monoalkyl ethers is inversely proportional to the length of the alkyl chain (methyl is more toxic than ethyl than propyl than butyl, etc.).

Given the methods of manufacture of the PEGs Cocamine, there is no likelihood of methoxyethanol, ethoxyethanol, etc., being present as impurities. In particular, because the PEGs Cocamine are PEG ethers of the primary aliphatic amine derived from coconut oil, and as such, are chemically different from the alkyl ethers, the Panel concluded there is no reproductive or developmental hazard posed by these compounds.

Polyethylene Glycol

No adverse reproductive effects occurred during subchronic (90 days) and chronic (2 years) oral toxicity studies of PEG-6-32 and PEG-75. In the subchronic study, PEG-75 was tested at a dose of 0.23 g/kg/day. In the chronic study, PEG-75 was tested at doses up to 0.062 g/kg/day and, PEG-6-32, at doses up to 1.69 g/kg/day (Andersen 1993).

MUTAGENICITY

PEG- 15 Cocamine was tested for mutagenicity using the paper-disk method. Nutrient agar was seeded with streptomycin dependent Sd-4-73 *Escherichia coli* and filter-paper disks containing PEG-15 Cocamine were placed on the surface of the cultures. The frequency of reversion from streptomycin dependence to independence was used as the measure of mutagenicity. PEG- 15 Cocamine was negative in this test (Szybalski 1958).

PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test; the maximum test concentration in both studies was 1%. In the unscheduled DNA synthesis assay, a statistically significant increase in radioactive thymidine incorporation into rat hepatocyte nuclei was noted only at the highest concentration tested (0.1% PEG-8). PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/l (Andersen 1993).

CARCINOGENICITY

All of the carcinogenicity data available on the PEGs were specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosing to rats; 1 year of dosing to mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

Coconut Oil was less effective than polyunsaturated fat as a tumor promoter for mammary tumors in rats induced by 7,12-dimethylbenz(l)anthracene (Elder 1986).

CLINICAL STUDIES

No clinical studies were available for the PEGs Cocamine polymers.

In clinical studies, PEG-6 and PEG-8 induced mild sensitization in 9% and 4% of 23 male subjects tested, respectively. However, later production lots of PEG-6, as well as PEG-75, did not cause reactions in any of the 100 male and 100 female subjects tested. A product formulation containing 3% PEG-8 induced minimal to mild irritation (induction phase) in over 75% of 90 volunteers participating in a skin irritation and sensitization study. Responses (not classified) were noted in 22 subjects at the 24-hour challenge reading. Cases of systemic toxicity and contact dermatitis in burn patients were attributed to PEG-based topical ointments. The ointment that induced systemic toxicity contained 63% PEG-6, 5% PEG-20, and 32% PEG-75 (Andersen 1993).

A variety of assays has been used in clinical assessments of cosmetic products containing Coconut Oil. Bar soaps containing 13% Coconut Oil, when tested using standard Draize procedures, produced very minimal skin reactions. In a 2-week normal-use test, bar soaps caused no unusual irritation response. The results of soap chamber tests of bar soaps were minimal irritation in one study and mild irritation in another. No phototoxicity or photosensitivity was produced by these same bar soap formulations. Additionally, there was no evidence of sensitization in studies of formulations containing 2.5% Coconut Oil or 10% Hydrogenated Coconut Oil (Elder 1986).

SUMMARY

PEG-2, -3, -5, - 10, - 15, and -20 Cocamine are the polyethylene glycol ethers of the primary aliphatic amine derived from coconut oil. These ingredients are surfactants which function as emulsifying and solubilizing agents in cosmetics. Product formulation data submitted to the FDA in 1996 indicate that only PEG-2, -3, -15, and -20 Cocamine are in use, and that they are used in 86 cosmetic formulations.

Little data on the PEGs Cocamine regarding metabolism, toxicity, mutagenicity, carcinogenicity, or clinical safety were available. Summary data on the PEGs and Coconut Oil were separately provided, with the view that these data were applicable to the PEG Cocamine compounds.

PEG Cocamine absorption and metabolism data were not available. PEG absorption is related to whether the substance is a liquid or a solid. PEGs were readily absorbed through damaged skin. Oral and intravenous studies on the PEGs indicated that these substances were excreted, unchanged, in the urine and feces. Ingested Coconut Oil was almost entirely absorbed with no mortality.

The oral LD50 value of PEG- 15 Cocamine in rats was 1.2 g/kg, and for PEG-2 Cocamine, values ranged from 0.75 g/kg to 1.3 g/kg. No systemic toxic effects occurred in rats following a 6-week dermal application study using 10% PEG- 15 Cocamine. PEGs have low oral and dermal toxicity; generally, the greater molecular weight PEGs appear to be less toxic than the lighter PEGs in oral studies. Coconut Oil and Hydrogenated Coconut Oil are relatively nontoxic by ingestion.

PEG-2 Cocamine was classified as a moderate cutaneous irritant, and PEG-15 Cocamine was considered a mild irritant. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer. Coconut Oil was not a skin irritant or a sensitizer. PEG-2 Cocamine was considered an ocular irritant, and PEG-15 Cocamine caused cornea1 irritation.

In mutagenicity studies, PEG-15 Cocamine was negative. PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. At concentrations up to 150 g/l, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the PEG Cocamine compounds would cause reproductive or teratogenic effects based on their structural characteristics. In subchronic and chronic feeding studies, PEG-6-32 and PEG-75 did not induce reproductive effects in rats.

In clinical studies, PEG-8 was a mild sensitizer and irritant. Contact dermatitis and systemic toxicity in bum patients were

attributed to a PEG-based topical ointment. Bar soaps containing 13% Coconut Oil, when tested using Draize procedures, produced minimal skin reactions.

DISCUSSION

Safety test data on the PEGs and on Coconut Oil and its derivatives were considered relevant and supportive of the safety of PEGs Cocamine polymers.

The CIR Expert Panel was concerned about the sensitization potential of the PEGs Cocamine (PEG-2, -3, -5, -10, -15, and -20 Cocamine) when applied to damaged skin. This concern arose because of positive patch tests and incidences of nephrotoxicity in bum patients treated with an antimicrobial cream that contained PEG-6, PEG-20, and PEG-75. PEG was determined to be the causitive agent in both animal and human studies; no evidence of systemic toxicity or sensitization was found in studies with intact skin. The Expert Panel concluded that cosmetic formulations containing PEG should not, therefore, be used on damaged skin.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. The Panel members stressed that the cosmetic industry should continue to use the necessary purification procedures to remove these impurities from the ingredients before blending them into cosmetic formulations.

Based on particle size and cosmetic use concentrations, it was not considered likely that these ingredients, in formulation, are respirable. Thus, the Expert Panel has no concerns regarding the absence of inhalation toxicity data, and the Panel considers the PEG Cocamine compounds safe for use in aerosolized products.

After considering the basic chemical structure of PEGs and the negative phototoxicity and photosensitization data on bar soaps containing Coconut Oil, the CIR Expert Panel concluded that it is unlikely that the PEGs Cocamine are either photosensitizers or phototoxic agents. As discussed in this report, the possibility of reproductive and developmental effects was assessed and determined not to be a concern.

Citing concerns about the amine in the cocamine moiety in these ingredients, the Panel determined that additional data were necessary. In addition, data specifically on PEG-2 Cocamine are needed to demonstrate that this smallest polymer in the group does not exhibit toxicity. 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 PEG-2, -3, -5, -10, -15, and -20 Cocamine were not sufficient for determining whether the ingredients, under relevant conditions of use, were either safe or unsafe. The Panel released an Insufficient Data Announcement on May 23, 1995, outlining the data needed to assess the safety of the PEG Cocamine compounds. Concentration of use data were received in reponse to the announcement. No other comments were received during the YO-day public comment period. Additional data needed to make a safety assessment are: (1) physical and chemical impurities, especially nitrosamines; (2) genotoxicity in a mammalian system; (3) 28-day dermal toxicity using PEG-2 Cocamine; and (4) dermal sensitization data on PEG-2 Cocamine.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of PEG-2, -3, -5, -10, -15, and -20 Cocamine for use in cosmetic products.

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