

Amended Final Report of the Safety Assessment of Cocamidopropylamine Oxide¹

Cocamidopropylamine Oxide is a tertiary amine oxide which functions as a hair-conditioning agent and as a surfactant, currently used in 60 cosmetic formulations at concentrations between 0.07% and 4.0%. In an earlier safety assessment, the Cosmetic Ingredient Review (CIR) Expert Panel had determined that the available data were insufficient to support the safety of this ingredient in cosmetic products. Additional data have now been provided and reviewed. Cocamidopropylamine Oxide was determined to have an acute oral LD₅₀ between 500 and 1000 mg/kg day⁻¹ using rats. The acute dermal LD₅₀ in rats was >2174 mg/kg day⁻¹. A 28-day repeated oral dose toxicity study in rats found hemolytic anemia at 150 and 1000 mg/kg day⁻¹, with a no observed effect level (NOEL) of 15 mg/kg day⁻¹. At 5%, Cocamidopropylamine Oxide solution was not a primary dermal irritant. Application of 81.5% Cocamidopropylamine Oxide to rabbit skin caused moderate irritation under Draize classification scale, but 81.5% Cocamidopropylamine Oxide in rabbit eyes caused severe irritation. A maximization study classified Cocamidopropylamine Oxide as a nonsensitizer to guinea pig skin. Cocamidopropylamine Oxide was not mutagenic in an Ames test, with and without metabolic activation. No evidence of increased chromosomal aberrations were noted in human lymphocytes treated with 81.5% Cocamidopropylamine Oxide. In a clinical study, 7.5% Cocamidopropylamine Oxide was not a sensitizer, although it did produce some reactions typical of mild irritation. Although the impurities, amidoamine and dimethylaminopropylamine, have been implicated in contact allergy reactions to products containing cocamidopropylamine betaine, clinical testing of a product with cocamidopropylamine betaine containing these impurities, at levels comparable to those found in Cocamidopropylamine Oxide, failed to produce a reaction in 10 individuals known to be sensitive to cocamidopropylamine betaine. Two repeat-insult patch tests using a facial wash with 1% raw material containing 35% to 36.5% Cocamidopropylamine Oxide did not find evidence of dermal sensitization. Tests for dermal phototoxicity and photoallergenicity with the same facial wash product also did not produce evidence of effect. The CIR Expert Panel recognizes that there are data gaps regarding the use and concentration of this ingredient. However, the overall information available on types of products in which this ingredient is used and at what concentration indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

Overall, these data demonstrate that Cocamidopropylamine Oxide has low toxicity in animal and in vitro tests. Although there are no available carcinogenicity data, the available genotoxicity data, combined with the absence of any structural alerts, suggest no carcinogenic potential. The Panel noted the absence of reproductive and developmental toxicity data. Because this ingredient has a highly polarized molecular structure, the Panel considered that it would be, at most, slowly absorbed. Given that most of the uses and the highest use concentration of 4% is found in rinse-off products, the Panel determined that the available data suggest that Cocamidopropylamine Oxide is safe as used in rinse-off products. Although dermal penetration may be slow, data on the extent of dermal penetration of Cocamidopropylamine Oxide are needed to support the safety of leave-on uses. If there is significant dermal absorption, dermal reproductive and developmental toxicity data may be needed.

INTRODUCTION

As described in the *International Cosmetic Ingredient Dictionary and Handbook*, Cocamidopropylamine Oxide is a tertiary amine oxide that functions as a hair-conditioning agent and as a surfactant in cleansing agents, foam boosters, and hydrotropes (Gottschalck and McEwen 2006).

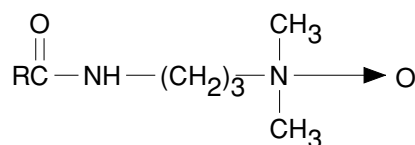
Cosmetic Ingredient Review (CIR) previously issued a safety assessment of Cocamidopropylamine Oxide as a cosmetic ingredient with the conclusion that the available data were insufficient to support safety (Andersen 2000).

Additional unpublished data have been provided and are presented, with the previously available data, in this amended safety assessment of Cocamidopropylamine Oxide.

CHEMISTRY

Definition and Structure

Cocamidopropylamine Oxide (CAS no. 68155-09-9) is a tertiary amine oxide that generally conforms to the formula:



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TABLE 1
Physical and chemical properties of Cocamidopropylamine Oxide

Property	Description	Reference
Physical characteristics	Clear to slightly hazy liquid (at 25°C)	Scher Chemicals, Inc. 1984
	Clear to slightly yellow virtually odorless liquid; 29.5% to 31.5% active	Nikitakis and McEwen 1990
	Supplied as a 30% or 35% aqueous solution	Janik and Podgórski 1988
Average molecular weight pH	320	Scher Chemicals, Inc. 1984
	6–8	Scher Chemicals, Inc. 1984
	6.5–8.0 at 25°C	Nikitakis and McEwen 1990
Solubility	Miscible with water, forms turbid suspensions with ethanol and acetone, immiscible with chloroform	Nikitakis and McEwen 1990
	Soluble in water and most hydrophilic solvents	Scher Chemicals, Inc. 1984
Specific gravity (25°C)	0.995	Scher Chemicals, Inc. 1984
Chemical composition		
Amine oxide	35% min.	Scher Chemicals, Inc. 1984
Free amine	0.5% max.	Scher Chemicals, Inc. 1984
	1.0% max.	Nikitakis and McEwen 1990
Free peroxide	0.5% max.	Scher Chemicals, Inc. 1984
	0.2% max.	Nikitakis and McEwen 1990
Residue on drying	29.5–34.0%	Nikitakis and McEwen 1990
Ionic nature	Solutions with pH \geq 7.0 are nonionic; solutions with pH < 7.0 are cationic	Scher Chemicals, Inc. 1984
Reactivity	Amine oxides are reported to be thermally unstable	Janik and Podgórski 1988

where RCO– represents the fatty acids from coconut oil (Gottschalck and McEwen 2006).

According to Kass (1979), Chemline (1996), and Gottschalck and McEwen (2006), Cocamidopropylamine Oxide is also known as:

- N-[3-(Dimethylamino)Propyl]Coco Amides-N-Oxide;
- Coco Amides, N-[3-(Dimethylamino)Propyl], N-Oxide;
- Amides, Coco, N-[3-(Dimethylamino)Propyl], N-Oxide;
- Amides, Coco, N-[3-(Dimethylamino)Propyl], N-Oxides;
- Cocamidopropyldimethylamine Oxide;
- Cocamidopropylmethylamine Oxide;
- Cocamido-3-Propyldimethylamine Oxide;
- 3-Cocamidopropyl Dimethylamine Oxide;
- 3-(N,N-Dimethylamino)Propyl Cocamido Amine Oxide;
- N-(Cocamidopropyl)-N,N-Dimethylamine Oxide;

- N,N-Dimethyl-N-(3-Cocamidopropyl)Amine Oxide; and
- N,N-Dimethyl-N-(3-(Coconut Oil Alkyl)Amidopropyl) Amine Oxide.

Physical and Chemical Properties

The physical and chemical properties of Cocamidopropylamine Oxide are described in Table 1. Published data on the ultraviolet absorbance of Cocamidopropylamine Oxide were not found.

Manufacture and Production

According to the Cosmetic, Toiletry, and Fragrance Association (CTFA), Cocamidopropylamine Oxide is produced by reacting hydrogenated coconut oil with dimethylamidopropylamine (DMAPA), which is further reacted with a food grade hydrogen peroxide (CTFA 1997).

Amine oxides are prepared via the reaction of a tertiary amine with hydrogen peroxide (Klein 1981). The oxidation reaction typically yields more than 90% product at 60°C to 80°C, and

the excess hydrogen peroxide is readily removed by using manganese dioxide plus filtration.

Analytical Methods

Janik and Podgórski (1988) used potentiometric titration in isopropyl alcohol and the combination of two-phase and titanometric titration for the simultaneous determination of amine oxide and unreacted amine, particularly with respect to the amine impurity, in commercial Cocamidopropylamine Oxide. The authors concluded that potentiometric titration was the better method.

Impurities

According to CTFA (1997), Cocamidopropylamine Oxide contains ≤ 3000 ppm free amidoamine and ≤ 5 ppm free DMAPA.

Commercial products made with amine oxides may contain “unreacted amine and various other products originating from different stages of synthesis” (Janik and Podgórski 1988).

USE

Cosmetic

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, Cocamidopropylamine Oxide functions as a hair-conditioning agent, surfactant—cleansing agent, surfactant—foam booster, and surfactant—hydrotrope (Gottschalck and McEwen 2006).

Janik and Podgórski (1988) stated that Cocamidopropylamine Oxide was the amine oxide most frequently used in various cosmetic formulations.

Voluntary product formulation data submitted by industry to the Food and Drug Administration (FDA) in 1997 included Cocamidopropylamine Oxide in a total of 55 cosmetic product formulations (FDA 1997). The total number of product formulations reported to the FDA in 2005 was 60 (FDA 2005).

Concentration of use data submitted by one supplier stated that Cocamidopropylamine Oxide, supplied as 35% active, is used at a typical range of 5% to 15%, i.e., 1.75% to 5.25% active (CTFA 1997). A 2005 industry survey found use concentrations between 0.07% and 4.0% active (CTFA 2005).

Available uses and concentrations as a function of product category are given in Table 2. The most recent use concentration data represents the current concentration of use.

According to the Japan Ministry of Health, Labor and Welfare (MHWL), Cocamidopropylamine Oxide is not included on the list of ingredients that must not be combined in cosmetic products that are marketed in Japan (MHLW 2005a), or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW 2005b); nor is its use restricted in the European Union (European Economic Community 2005).

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

Published data on the absorption, distribution, metabolism, or excretion of Cocamidopropylamine Oxide were not found, although its solubility (soluble in water, only miscible in organic solvents) as given in Table 1 suggests low dermal penetration.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Safepharm Laboratories, Ltd. (2000a) conducted an acute oral toxicity study of a product containing 81.5% Cocamidopropylamine Oxide on Sprague-Dawley CD rats. A single oral dose of 2174 mg/kg body weight of test material (approximately 1772 mg/kg body weight of pure Cocamidopropylamine Oxide) was administered in a solution of distilled water to three fasted females. Two of the animals were found dead 1 to 2 days post dosing. These results led to further groups (numbers, age, and sex unknown) being administered a dose of 218 mg/kg body weight of test material (corrects to 178 mg/kg body weight pure material). At the end of the study, surviving animals were killed by cervical dislocation and subjected to gross necropsy.

Clinical signs of toxicity in the group of rats given the 2174 mg/kg body weight dose included hunched posture, diarrhea, increased salivation with incidents of pallor of extremities, emaciation, lethargy, piloerection, decreased respiratory rate, labored respiration, red/brown staining around the snout, and tiptoe gait. At necropsy, abnormalities observed in this dose group included hemorrhagic lungs, gastric mucosa, and small and large intestines; dark liver and kidneys; and sloughing and/or hemorrhage of nonglandular stomach epithelium. Animals in the 218 mg/kg body weight dose group had no deaths during the observation period and appeared normal throughout the study. The acute oral LD₅₀ was determined to be between 178 and 1772 mg/kg of pure Cocamidopropylamine Oxide (Safepharm 2000a).

Acute Dermal Toxicity

Safepharm (2000b) evaluated the dermal toxicity of a material containing 81.5% Cocamidopropylamine Oxide using a group of 10 Sprague-Dawley CD rats (five males and five females). The material was administered to intact skin in a single 24-h, semioccluded dermal application of 2174 mg/kg body weight (approximately 1772 mg/kg body weight pure material). The animals were observed for 14 days after the application, then killed for gross pathologic examination.

No animals died during the observation period, nor were signs of systemic toxicity noted. Dermal irritation ranged from very slight to well-defined erythema, with very slight edema, light brown discoloration of epidermis, desquamation, bleeding, crust formation, and glossy skin. No abnormalities were detected at necropsy. The LD₅₀ was determined to be greater than 2174 mg/kg body weight (Safepharm 2000b).

TABLE 2
Historical and current cosmetic product uses and concentrations for Cocamidopropylamine Oxide

Product category	1997 uses (Andersen 2000)	2005 uses (FDA 2005)	1984 concentrations (FDA 1984) (%)	2005 concentrations (CTFA 2005) (%)
Bath				
Soaps and detergents	1	3	1.0–5.0	4.0
Oils, tablets, and salts	—	2	—	—
Bubble baths	2	2	—	—
Other bath preparations	3	3	0.1–1.0, 10.0–25.0	—
Eye Makeup				
Eye makeup remover	—	—	—	0.02
Noncoloring Hair Care				
Conditioners	3	4	—	—
Permanent waves	1	2	—	0.007
Shampoos	25	24	0.1–10.0	0.5–3.0
Tonics, dressings, etc.	4	4	—	—
Other hair preparations	3	3	—	—
Hair Coloring				
Hair dyes and colors	2	3	—	—
Shampoos	2	1	—	—
Nail Care				
Other manicuring preparations	1	1	—	—
Personal Hygiene				
Underarm deodorants	—	1	—	—
Other personal hygiene products	1	1	—	4.0
Skin Care				
Cleansing creams, lotions, liquids, and pads	6	6	—	—
Other skin care preparations	1	—	—	—
Total uses/ranges for Cocamidopropylamine Oxide	55	60	0.1–25.0	0.07–4.0

Short-Term Oral Toxicity

A 28-day repeated oral dose toxicity study was performed by Safepharm (2000c) using Sprague-Dawley Crl:CD BR rats. A solution of 81.5% Cocamidopropylamine Oxide in distilled water was administered by gavage to three groups of animals (five males and five females, each) at dose levels of 15, 150, or 1000 mg/kg/day (dose was corrected for the 81.5% purity of test material). A control group of five males and five females were dosed with the distilled water vehicle. During the administration period, the animals were monitored for clinical signs, functional observations, body weight development, and food and water consumption. The hematology and blood chemistry was evaluated for all the rats at the end of the study. Gross necropsy and histopathological evaluations of selected tissues were also conducted at the end of the study.

Animals in the 1000 mg/kg/day dose group had clinical signs of toxicity from day 3 to the end of the study. Fur loss, noisy respiration, increased salivation, red/brown staining of fur, wet fur, and hunched posture were observed. Sporadic signs of diuresis,

staining of the anogenital region, tiptoe gait, gasping respiration, and pallor of extremities were also noted. One female in this group died on day 12 after exhibiting staining of the snout and mouth, dehydration, piloerection, and respiratory pattern change.

In the 1000 mg/kg/day dose group, significant elevation in neutrophil numbers were noted as were elevations in plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. AST and ALT activities (but not bilirubin) were increased significantly in the 150 mg/kg/day group, but no liver damage was reported. Both groups had an increase in spleen weight and absolute and relative body weight, but the increases in the 150 mg/kg/day group were not significant. The no observed effect level (NOEL) was determined to be 15 mg/kg/day (Safepharm 2000c).

Dermal Irritation

The dermal irritation potential of 5.0% Cocamidopropylamine Oxide was determined using six albino rabbits (Leberco

Laboratories 1985). The test material was applied for 24 h under occlusive patches to a clipped area of the back; 0.5 ml was applied to both an abraded site and an intact site. The sites were evaluated for irritation immediately and 24 h after patch removal. The primary irritation score was 1.41, indicating the potential for mild irritation. The 5% active Cocamidopropylamine Oxide solution was “not a primary dermal irritant.”

Safepharm (2000d) evaluated the dermal irritation potential of 81.5% Cocamidopropylamine Oxide using New Zealand white rabbits. A single 4-h, semioccluded application of test material was applied to the intact skin of three rabbits and produced well-defined erythema, slight edema, loss of skin elasticity and flexibility, crust formation, and slight desquamation. Semioccluded applications of 3-min and 1-h duration to intact skin of one rabbit produced no observable signs of skin irritation. The test material was classified as a moderate irritant to rabbit skin according to the Draize classification scheme.

Skin Sensitization

A Magnusson and Kligman maximization study was performed by Safepharm (2000e) to determine the sensitization potential of 81.5% Cocamidopropylamine Oxide in albino guinea pigs. In the induction phase, 20 animals (an additional 10 animals served as controls) were given intradermal injections of the material (0.1% w/w in distilled water). A topical solution of the concentration 75% w/w in distilled water was then applied. The guinea pigs were then challenged with a topical solution (5% and 2% w/w in distilled water). The sensitization rate produced was 0% and Cocamidopropylamine Oxide was classified as a nonsensitizer to guinea pig skin.

Ocular Irritation

Safepharm (2000f) reported the irritancy potential of 81.5% Cocamidopropylamine Oxide in New Zealand white rabbits. A single application (amount unknown) of the material to the non-irrigated eye of one rabbit produced opalescent corneal opacity, iridial inflammation, and severe conjunctival irritation. Dulling of the normal luster of the cornea and vascularization was noted along with a localized vessel ingrowth of 1 to 2 mm. After 14 days of observation, the treated eye appeared normal. Cocamidopropylamine Oxide at 81.5% concentration was considered to be a severe irritant to the rabbit eye.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of Cocamidopropylamine Oxide were not found.

GENOTOXICITY

Safepharm (2000g) evaluated the mutagenicity of 81.5% Cocamidopropylamine Oxide using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2uvrA at doses of 15, 50, 100, 150, 200, and 500

μg/plate, with and without metabolic activation. The first toxic responses were noted at 200 μg/plate without metabolic activation and at 500 μg/plate with metabolic activation. No toxicologically significant increases in frequency of revertant colonies were observed in any strains with any dose (with or without metabolic activation). Cocamidopropylamine Oxide was considered to be nonmutagenic.

Safepharm (2000h) treated human lymphocytes with three unknown dose amounts of 81.5% Cocamidopropylamine Oxide and looked for chromosome aberrations *in vitro*. Controls for vehicle and positive results were also studied. The test material did not induce any statistically significant increases in aberration frequency in cells, with and without metabolic activation (excluding gaps). The report concluded that Cocamidopropylamine Oxide is nonclastogenic to human lymphocytes.

CARCINOGENICITY

Published data on the carcinogenic potential of Cocamidopropylamine Oxide were not found.

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

Harrison Research Laboratories, Inc. (1993) performed a repeat-insult patch test study using a facial wash (1% raw material which contained 35% to 36.5% Cocamidopropylamine Oxide). Out of the 252 subjects empaneled (age range from 18 to 65), 199 subjects completed the study. During the induction phase, three subjects scored ± (faint, minimal erythema). During the challenge phase, 24 subjects scored ± and 6 subjects scored a 1 (erythema). It was concluded that the test material did not induce contact dermal sensitization in human subjects.

International Research Services, Inc. (1997) performed a modified Draize assay using a test product containing 7.5% Cocamidopropylamine Oxide. Of the original 120 subjects, 110 completed the study. During induction, 0.025 g of the test material was applied to the scapular area of the back under occlusive patches. A total of 10 applications were made. Forty-eight hours after patch application (72 h on weekends), the patches were removed and the test sites were rinsed and evaluated. New patches were then applied. Twelve days after removal of the last patch, a challenge patch with the same dose used during induction was applied to a previously untested site. The challenge patch was removed 48 h after application, and the site was evaluated 48 and 96 hours after application.

During the induction phase of the study, 1+ reactions (erythema throughout the entire patch area) were observed in 53 subjects and 2+ reactions (erythema and edema) were observed in three subjects. These reactions were considered typical of mild irritation. Two of the subjects had 1+ reactions at the 48- and 96-h challenge readings. The researchers concluded that “no evidence of sensitization” to 7.5% Cocamidopropylamine Oxide was observed (International Research Services, Inc. 1997).

As noted earlier, amidoamine at ≤ 3000 ppm and DMAPA at ≤ 5 ppm are impurities in Cocamidopropylamine Oxide. These chemicals are also impurities in cocamidopropylamine betaine and have been implicated as causative agents in contact allergy reactions to cocamidopropylamine betaine (Fartasch et al. 1999).

Fartasch et al. (1999) evaluated reactions of 10 individuals with a history of contact allergy to cocamidopropylamine betaine (CAPB) to a CAPB-based shower gel at 25% concentration that contained amidoamine at $<0.1\%$ and DMAPA at <10 ppm. None of the subjects had a positive allergic reaction. Further testing directly with three different concentrations of cocamidopropylamine betaine and dimethylamino-propylamine (0.1%, 0.3%, and 1%) produced positive allergic reactions to cocamidopropylamine betaine in half the individuals at the 1% concentration, but none at the lower concentrations, and to only one individual with DMAPA who reacted to all three concentrations.

Harrison Research Laboratories, Inc. (2001a) conducted a repeat-insult patch test using a facial wash (1% raw material containing 35% to 36.5% Cocamidopropylamine Oxide). Of the 215 subjects enrolled, 189 completed the study (ages ranged from 18 to 70). The test material (0.2 ml) was dispensed onto the semi-occlusive webril/adhesive patch, and placed on the left side of the back. Each subject removed the patch 24 h later, and the procedure was repeated after a 24-h nonapplication period (48 h on the weekends) for a total of nine induction patches. The test site was observed for any signs of reaction and recorded at the time a new patch was reapplied. During these observations, two \pm reactions (faint, minimal erythema) were noted at the first reading.

The subjects were given a 2-week period of non-treatment, which was followed by the challenge dose. The challenge patch was applied to the right side of the back for 24 h. The site was observed for a reaction immediately after removal and again 48, 72, and 96 h after application. During this phase, only one \pm reaction was noted at the 48-h postapplication observation. It was concluded that Cocamidopropylamine Oxide did not induce dermal sensitization (Harrison Research Laboratories, Inc. 2001a).

Photoallergenicity

Harrison Research Laboratories, Inc. (2001b) evaluated the potential for a facial wash (1% raw material containing 35% to 36.5% Cocamidopropylamine Oxide) to induce dermal photoallergenicity in human subjects. Twenty-nine subjects enrolled in the study, and 28 completed it (ages ranged from 33 to 69). Approximately 0.2 ml of test material was applied to each patch and placed on the subject's volar forearm. The same arm had a control patch that had no test material and a patch with test material was placed on the opposite arm or back, which was not irradiated.

Twice a week, for the first 3 weeks, patches were applied to the identical sites for a total of six induction patchings. Twenty-four hours after application, the patches were removed and scored and the subjects were irradiated with both ultraviolet A and B

(UVA and UVB). Immediately afterwards, the test sites were scored and recorded.

Subjects were exposed to the UVA radiation source for 17 min (total of 3.2 ± 0.3 J; 95% of the output for the UVA light was in a wavelength range between 320 and 400 nm). The UVB radiation source had an output in the range of 280 to 320 nm. The duration of exposure was based on each subject's skin type and minimal erythema dose as determined by the first irradiation.

A challenge phase followed a 2-week rest period, in which a patch was placed on a virgin site for 24 h. The sites were irradiated with UVA light only and reactions were scored immediately. Subjects were observed 48 and 72 h post patching for scoring.

During the induction phase, low-level, transient reactions (minimal erythema to erythema within patch margins) occurred at the irradiated test material and control patch sites. Both irradiated sites were also observed to have slight tanning responses.

At the challenge stage, no reactions were observed on either irradiated or nonirradiated test sites. No reactions occurred on the irradiated control site. The facial wash containing Cocamidopropylamine Oxide did not induce dermal photoallergy or dermal sensitization in humans (Harrison Research Laboratories, Inc. 2001b).

Phototoxicity

Harrison Research Laboratories, Inc. (2001c) evaluated the potential of a facial wash, 1% raw material that contained 35% to 36.5% Cocamidopropylamine Oxide, to induce a phototoxic response in human subjects. Ten subjects participated in the study in which a webril/adhesive patch was used semiocclusively. A patch containing approximately 0.2 ml of the test material was adhered to the subject's volar forearm for irradiation. Another patch containing test material was adhered to the subject's opposite arm or back but was not irradiated. The patches were worn for 24 h, and then were exposed to UVA (95% output in a wavelength range between 320 and 400 nm) for 17 min (total of 3.2 ± 0.3 J). All subjects were observed and reactions were scored. At 48 and 72 h post patching, the subjects were observed again and reactions were scored. There were no visible reactions in subjects except for some dryness in one female subject at the irradiated site at 48 and 72 h after the test material was applied. It was concluded that the facial wash did not induce a dermal phototoxic response in humans.

SUMMARY

Cocamidopropylamine Oxide is a tertiary amine oxide that functions as a hair-conditioning agent and as a surfactant. One analysis of Cocamidopropylamine Oxide, 35% active, reported $\leq 0.3\%$ free amidoamine and ≤ 5 ppm DMAPA. In 2005, voluntary industry reports to the FDA indicated that Cocamidopropylamine Oxide was used in 60 cosmetic formulations. A 2005 survey of industry use found active concentrations between 0.07% and 4.0%.

Cocamidopropylamine Oxide was determined to have an acute oral LD₅₀ between 178 and 1772 mg/kg body weight using rats. The acute dermal LD₅₀ using rats was determined to be greater than 1772 mg/kg body weight.

A 28-day repeated oral dose toxicity study in rats found toxicologically significant effects at 150 and 1000 mg/kg/day. At the high dose, significant elevation in neutrophil numbers were noted, as were elevations in plasma AST, ALT, and bilirubin. AST and ALT activities (but not bilirubin) were increased significantly in the 150 mg/kg group. The NOEL was 15 mg/kg/day.

A 5% active Cocamidopropylamine Oxide solution was not a primary dermal irritant. Application of 81.5% Cocamidopropylamine Oxide to rabbit skin caused moderate irritation under Draize classification scale. A maximization study classified Cocamidopropylamine Oxide as a nonsensitizer to guinea pig skin.

Treatment with 81.5% Cocamidopropylamine Oxide in rabbit eyes caused severe irritation.

Cocamidopropylamine Oxide was not mutagenic in an Ames test using *Salmonella Typhimurium* and *Escherichia coli*, both with and without metabolic activation. No evidence of increased chromosomal aberrations were noted in human lymphocytes treated with 81.5% Cocamidopropylamine Oxide.

In a clinical test, 7.5% Cocamidopropylamine Oxide was not a sensitizer, although it did produce some reactions typical of mild irritation.

Cocamidopropylamine Oxide impurities, including amidoamine and dimethylaminopropylamine, have been implicated in contact allergy reactions to products containing cocamidopropylamine betaine. Clinical testing of a product with cocamidopropylamine betaine containing these impurities, at levels comparable to those found in Cocamidopropylamine Oxide, failed to produce a reaction in 10 individuals known to be sensitive to cocamidopropylamine betaine.

Two repeat-insult patch tests using a facial wash with 1% raw material containing 35% to 36.5% Cocamidopropylamine Oxide did not find evidence of dermal sensitization. Tests for dermal phototoxicity and photoallergenicity with the same facial wash product also did not produce evidence of effect.

DISCUSSION

In its earlier safety assessment, the CIR Expert Panel had determined that the available data were insufficient to support the safety of Cocamidopropylamine Oxide in cosmetic products. Several data needs were identified and additional data were provided and reviewed. These data demonstrate that Cocamidopropylamine Oxide has low toxicity in animal tests. In one short-term oral toxicity study using rats, however, a NOEL of 15 mg/kg was determined, with effects at 150 and 1000 mg/kg. Because this was an oral toxicity study, and many exposures to this ingredient in cosmetics would be rinse-off topical formulations, the likely dermal absorption was considered. Because Cocamidopropylamine Oxide is soluble in water and only mis-

cible in organic solvents, low dermal penetration is suggested from topical rinse-off formulations.

Cocamidopropylamine Oxide was not mutagenic in an Ames assay, with or without metabolic activation, nor was it clastogenic in a human lymphocyte assay. These data, combined with the absence of any structural alerts, suggest no carcinogenic potential.

Cocamidopropylamine Oxide at high concentrations is a dermal and ocular irritant, but it is not a sensitizer. Clinical testing did not detect dermal sensitization, and confirmed that this ingredient is neither a photosensitizer nor is it phototoxic.

The Panel noted the absence of reproductive and developmental toxicity data. Because this ingredient has a highly polarized molecular structure, the Panel considered that it would be, at most, slowly absorbed. Given that most of the uses and the highest use concentration of 4% is found in rinse-off products, the Panel determined that the available data suggest that Cocamidopropylamine Oxide is safe as used in rinse-off products.

The CIR Expert Panel recognized that there are data gaps regarding the use and concentration of this ingredient. However, the overall information available on types of products in which this ingredient is used and at what concentration indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

For leave-on uses, while dermal penetration may be slow, data on the extent of dermal penetration of Cocamidopropylamine Oxide are needed to support the safety of leave-on uses. If there is significant dermal absorption, dermal reproductive and developmental toxicity data may be needed.

CONCLUSION

Based on the data contained in this report, the CIR Expert Panel concluded that Cocamidopropylamine Oxide is safe as a cosmetic ingredient in rinse-off cosmetic products in the practices of use and concentrations described in this safety assessment, but the data are insufficient to make a determination of safety for use in leave-on cosmetic products.

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