Final Report on the Safety Assessment of Cocamidopropylamine Oxide[1]

Cocamidopropylamine Oxide is a tertiary amine oxide used in a wide variety of cosmetic formulations. This ingredient functions as a hair conditioning agent, surfactant—cleansing agent, surfactant—foam booster, and surfactant—hydrotrope. It may be supplied as 35% active ingredient, and be used at concentrations between 5% and 15%. As supplied, it contains ≤0.3% free amidoamine and ≤5 ppm dimethylamidopropylamine. As a class, amine oxides are reported to be relatively nontoxic. The oral LD_{50} values of amine oxides range from 2 to 6 g/kg. A 5% active Cocamidopropylamine Oxide solution was not a primary dermal irritant in rabbits. Amine oxides are reported to be nonirritating to the skin and eyes at 2% and mildly irritating at 10%. In a clinical study, Cocamidopropylamine Oxide was not a sensitizer, although some mild irritation was produced during the induction phase. These data were not considered adequate to complete a safety assessment of this ingredient. Additional data needed include: (1) Ultraviolet (UV) absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed; (2) Dermal absorption data; if dermal absorption occurs, 28-day dermal toxicity and reproductive and developmental toxicity are needed; and (3) two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods is needed. Until these data are provided, the available data are insufficient to support the safety of Cocamidopropylamine Oxide for use in cosmetic products.

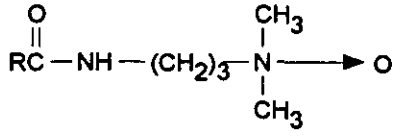
INTRODUCTION

Cocamidopropylamine Oxide is a tertiary amine oxide that functions as a hair conditioning agent, surfactant—cleansing agent, surfactant—foam booster, and surfactant—hydrotrope (Wenninger, Canterbery, and McEwen 2000).

CHEMISTRY

Definition and Structure

Cocamidopropylamine Oxide (CAS No. 68155-09-9) is a tertiary amine oxide that generally conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



where RCO– represents the fatty acids from coconut oil.

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 (Wenninger, Canterbery, and McEwen 2000); Amides, Coco, *N*-[3-(Dimethylamino) Propyl], *N*-Oxides; Cocamidopropyldimethylamine Oxide (Kass 1979); Cocamidopropylmethylamine Oxide; Cocamido-3-Propyldimethylamine Oxide; 3-Cocoamidopropyl Dimethylamine Oxide; 3-(*N*, *N*-Dimethylamino)Propyl Cocamido Amine Oxide; *N*-(Cocamidopropyl)-*N*, *N*-Dimethylamine Oxide; *N*, *N*-Dimethyl-*N*-(3-Cocamido-propyl)Amine Oxide; and *N*, *N*-Dimethyl-*N*-(3-(Coconut Oil Alkyl)Amidopropyl) Amine Oxide (Chemline 1996).

Physical and Chemical Properties

The physical and chemical properties of Cocamidopropylamine Oxide are described in Table 1.

Manufacture and Production

Cocamidopropylamine Oxide is produced by reacting hydrogenated coconut oil with dimethylamidopropylamine (DMAPA) (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1997). This is then further reacted with a food grade hydrogen peroxide.

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 to 80°C, and the excess hydrogen peroxide is readily removed by using manganese dioxide plus filtration.

Analytical Methods

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

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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%–31.5% active	Nikitakis and McEwen 1990
	Supplied as a 30% or 35% aqueous solution	Janik and Podgórski 1988
Average molecular weight	320	Scher Chemicals, Inc. 1984
pH	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	
Free peroxide	0.5% max	
Free amine	1.0% max	Nikitakis and McEwen 1990
Peroxide (as H_2O_2)	0.2% max	
Residue on drying	29.5%–34.0%	
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

Ultraviolet Absorbance

Published data on the ultraviolet absorbance of Cocamidopropylamine Oxide were not found.

Impurities

Analysis of Cocamidopropylamine Oxide reported $\leq$0.3% free amidoamine and $\leq$5 ppm free DMAPA (CTFA 1997).

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

USE

Cosmetic

Cocamidopropylamine Oxide was reported to be the amine oxide most frequently used in various cosmetic formulations (Janik and Podgórski 1988). The product formulation data submitted to the Food and Drug Administration (FDA) in 1997 stated that Cocamidopropylamine Oxide was contained in a total of 55 cosmetic product formulations (FDA 1997) (Table 2).

Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). However, 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%, that is, 1.75% to 5.25% active (CTFA 1997). The product formulation data submitted to the FDA in 1984 (FDA 1984) reported that Cocamidopropylamine Oxide was used at concentrations of $\leq$25% (Table 3).

International

Cocamidopropylamine Oxide is not listed in Annex II (list of substances which must not form part of the composition of cosmetic products) or Annex III (list of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down) of the Cosmetics Directive of the European Union (European Economic Community 1995). It is also not listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category* (Rempe and Santucci 1997).

GENERAL BIOLOGY

Published data on Cocamidopropylamine Oxide which would normally be summarized in the General Biology section, such as absorption, distribution, and metabolism data, were not found.

ANIMAL TOXICOLOGY

Amine oxides are reported to be relatively non-toxic at use concentrations (Klein 1981). Their LD_{50} values range from 2 to 6 g/kg of the concentrated product.

Dermal Irritation

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

TABLE 2
Product formulation data (FDA 1997)

Product category	Total no. of formulations in category	Total no. containing ingredient
Bubble baths	186	2
Other bath preparations	141	3
Hair conditioners	596	3
Permanent waves	297	1
Shampoos (noncoloring)	825	25
Tonics, dressings, and other hair grooming aids	512	4
Other hair preparations	311	3
Hair dyes and colors	1478	2
Hair shampoos (coloring)	17	2
Other manicuring preparations	59	1
Bath soaps and detergents	341	1
Other personal cleanliness products	262	1
Cleansing preparations	630	6
Other skin care preparations	683	1
1997 total		**55**

(Leberco Laboratories 1985). The test material was applied for 24 hours under occlusive patches to a clipped area of the back; 0.5 ml was applied to an abraded site and 0.5 ml was applied to an intact site. The sites were evaluated for irritation immediately and 24 hours 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."

Amine oxides are nonirritating to the skin at 2% and are mildly irritating at 10% (Klein 1981).

Sensitization

Published data on the sensitization potential of Cocamidopropylamine Oxide using animals were not found.

Ocular Irritation

Amine oxides are nonirritating to the eyes at 2% and are mildly irritating at 10% (Klein 1981).

TABLE 3
Concentration of use data (FDA 1984)

Product category	10%–25%	5%–10%	1%–5%	0.1%–1%	Total
Other bath preparations	2			1	3
Shampoos (noncoloring)		1	26	1	28
Bath soaps/ detergents			1		1
Total	**2**	**1**	**27**	**2**	**32**

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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

MUTAGENICITY/CARCINOGENICITY

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

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

As noted earlier, amidoamine at $\leq$0.3% and dimethylaminopropylamine at $\leq$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). Using cocamidopropylamine betaine with amidoamine at <0.1% and dimethylaminopropylamine at <10 ppm in a shower gel (Fartasch et al. 1999) exposed 10 individuals with a history of contact allergy to cocamidopropylamine betaine. None of the subjects had a positive allergic reaction. Further testing directly with three different concentrations of cocamidopropylamine betaine and dimethylaminopropylamine (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 dimethylaminopropylamine, who reacted to all three concentrations.

A modified Draize assay was performed to determine the sensitization potential of 7.5% Cocamidopropylamine Oxide in a test product and was completed with 110 of 120 initial subjects

(International Research Services, Inc. 1997). 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 was made. Forty-eight hours after patch application (72 hours 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 hours after application, and the site was evaluated 48 and 96 hours after application. During the induction phase of the study, 164 1+ reactions (erythema throughout the entire patch area) were observed in 53 subjects and five 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-hour challenge readings. The researchers concluded that "no evidence of sensitization" to 7.5% Cocamidopropylamine Oxide was observed.

SUMMARY

Cocamidopropylamine Oxide is a tertiary amine oxide which functions as a hair conditioning agent and as a surfactant. One analysis of Cocamidopropylamine Oxide, 35% active, reported ≤0.3% free amidoamine and ≤5 ppm DMAPA. In 1997, it was reported to the FDA that Cocamidopropylamine Oxide was used in 55 cosmetic formulations. One supplier reported that Cocamidopropylamine Oxide, supplied as 35% active, is used at concentrations of 5% to 15%; in 1984, Cocamidopropylamine Oxide was reported to be used at concentrations of ≤25%.

The LD_{50} values of amine oxides range from 2 to 6 g/kg of the concentrated product. A 5% active Cocamidopropylamine Oxide solution was not a primary dermal irritant. Amine oxides are nonirritating to the skin or eyes at 2%, and were mildly irritating at 10%.

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.

DISCUSSION

Section 1, paragraph (p), of the CIR Procedures states that "A lack of information about an ingredient shall not be enough 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 Cocamidopropylamine Oxide were insufficient to determine whether Cocamidopropylamine Oxide, for purposes of cosmetic use, is either safe or unsafe. The Expert Panel released a "Notice of Insufficient Data Announcement" on December 17, 1996 outlining the data needec to assess the safety of Cocamidopropylamine Oxide. Cocentration of use data, method of manufacture, impurities data, and a skin sensitization study were received, but an offer to supply the remaining data was not. The types of data still required include:

1. UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed.
2. Dermal absorption data; if dermal absorption occurs, 28-day dermal toxicity and developmental toxicity data are needed.[2]
3. Two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed according to NTP standards is needed.

In accordance with Section 45 of the CIR Procedures, the Expert Panel issued a Final Report—Insufficient Data. When the remaining requested data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report. The Expert Panel noted that if the needed data are submitted but do not support a concentration greater than 5%, the concentration of use for leave-on products would be limited to 5% based on irritation data currently summarized in the report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Cocamidopropylamine Oxide for use in cosmetic products.

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[2]Although the CIR Expert Panel has specified a "28-day dermal toxicity study," there is concern that specifying a type of study may inhibit those who want to gather data using other study designs. The types of data the Panel is seeking include the gross pathology and histopathology in skin and other major organ systems, along with certain other toxicity parameters, associated with repeated exposures. Doing a 28-day dermal toxicity study would generate the needed data. But there are other approaches. For example, the Expert Panel would consider a dermal reproductive and developmental toxicity study in which gross pathology and histopathology data are gathered on the F_0 generation to be sufficient to meet the "28-day dermal toxicity and dermal developmental/reproductive data" requested in item 2, if done at or above current concentrations of use of the ingredient.

[3]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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