FINAL REPORT ON THE SAFETY ASSESSMENT OF CETYL ESTERS[1]

Cetyl Esters is a synthetic wax composed of a mixture of esters of saturated fatty acids and fatty alcohols with carbon chain lengths between 14 and 18. Cetyl Esters is currently used as a skin conditioning agent–emollient in over 200 cosmetic formulations at concentrations of up to 7%. The esters that are found in Cetyl Esters include Cetyl Palmitate, Cetyl Stearate, Myristyl Myristate, Myristyl Stearate, Cetyl Myristate, and Stearyl Stearate. Safety data on four of these (Cetyl Palmitate, Cetyl Stearate, Myristyl Myristate, and Myristyl Stearate) have previously been reviewed and are summarized in this report; overall, the data show no systemic toxicity, no sensitization or photosensitization, and little irritation. Because of the structural similarity of Cetyl Myristate and Stearyl Stearate to these four ingredients, it is expected that they would behave in a similarly nontoxic manner. Therefore, it was concluded that Cetyl Esters (as a mixture of all six ingredients) is safe as used in cosmetics.

The following is a compilation of data concerning Cetyl Esters. Cetyl Esters is a synthetic mixture consisting of esters of saturated fatty acids and fatty alcohols; the fatty acids and alcohols have carbon chain lengths between 14 and 18. A synonym for Cetyl Esters is synthetic spermaceti wax (National Formulary, 1990; Nikitakis and McEwen, 1990; Wenninger and McEwen, 1995a).

Within the National Formulary definition, there are nine esters that fit the specifications. One industry source reports that of these nine, three (Myristyl Palmitate, Stearyl Palmitate, and Stearyl Myristate) are not found in any commercial Cetyl Esters preparation. The source reports Cetyl Esters to be comprised of a mixture of one or more of the following six esters: Cetyl Palmitate, Myristyl Myristate, Cetyl Stearate, Myristyl Stearate, Cetyl Myristate, and Stearyl Stearate (Cosmetic, Toiletry and Fragrance Association [CTFA], 1995). Of these six, the first four have been reviewed by the Cosmetic Ingredient

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

Bindu Nair, Scientific Analyst and Writer, prepared this report.

Address correspondence to Dr. F. Alan Andersen, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

International Journal of Toxicology, 16 (Suppl. 1):123–130, 1997

1091-5818/97 $12.00 + .00

Review (CIR) Expert Panel and found to be safe as used (Elder 1982a, 1982b, 1985). The expected concentration of use in cosmetics of these four are Cetyl Palmitate (10%), Myristyl Myristate (25%), Cetyl Stearate (10%), and Myristyl Stearate (5%).

Following a Notice to Proceed (without preparing a Scientific Literature Review), the CIR Expert Panel decided to continue its review of Cetyl Esters, with use of the findings of the earlier reports. Adaptions from these earlier reviews appear in this report in an italicized font. In addition, because these reviews were completed more than 10 years ago, an updated computer literature search was performed. No studies relevant to the safety assessment have been published since the CIR review.

DEFINITION AND STRUCTURE

Cetyl Esters is a synthetic wax with a composition and properties identical to natural spermaceti wax (Wenninger and McEwen, 1995a). The structure of the six esters that can be present in a Cetyl Esters preparations are shown in Figure 1.

PHYSICAL AND CHEMICAL PROPERTIES

Cetyl Esters is described as a somewhat translucent white to off-white solid with a crystalline structure. It has a faint odor and a bland mild

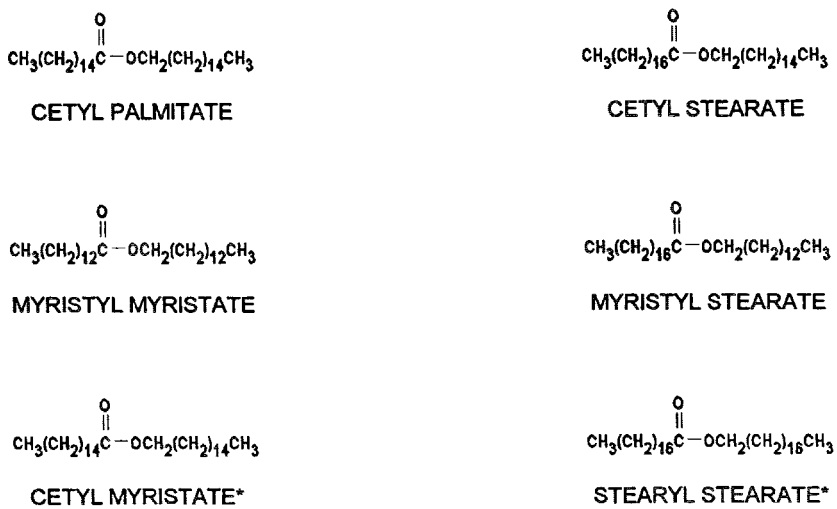

Figure 1. Structure of the six esters found in Cetyl Esters. *Not previously reviewed by CIR.

taste. It is soluble in boiling alcohol, ether, chloroform, and fixed oils and is insoluble in water and cold alcohol. It has a specific gravity range of 0.820 to 0.840 at 50°C, a melting range between 43° and 47°C, and a saponification value of 109 to 120 (Nikitakis and McEwen, 1990).

USE

Cosmetic

Cetyl Esters is used in cosmetic formulations as a skin-conditioning agent–emollient (Wenninger and McEwen, 1995b). As of January 1995, there were 210 reported uses of Cetyl Esters in various cosmetics (Food and Drug Administration [FDA], 1995; Table 1).

Concentrations of use are no longer reported to the FDA (FDA, January 1992). Data submitted directly to CIR from the cosmetics industry indicate that Cetyl Esters is used at concentrations of up to 7% in both leave-on and rinse-off cosmetic formulations (CTFA, 1995).

GENERAL BIOLOGY

The Myristates, Palmitates, and Stearates can undergo chemical or enzymatic hydrolysis to myristic acid, palmitic acid, and stearic acid (and the corresponding alcohols), respectively. Transesterification and other typical ester reactions may also occur. All of these esters are saturated compounds and would not be expected to autoxidize readily.

Myristic acid is a digestible constituent of most vegetables and animals and is nontoxic when ingested. When myristic acid was fed to dogs (as the ethyl ester), less than 2% of the amount fed was recovered as unabsorbed material in the feces; there was no increase in ether-soluble acids in the urine. The palmitates would be expected to be nontoxic in view of their hydrolysis to palmitic acid (Elder, 1982a, 1982b, 1985).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The oral LD_{50} in CFW mice of the Carworth strain of a trade product composed of 60% to 65% of Cetyl Esters in corn oil was more than 20 g/kg (Leberco Laboratories, 1971a). Another source reported the oral LD_{50} in hairless mice for Cetyl Palmitate was more than 5000 mg/kg (Henkel Department of Toxicology, 1974).

Myristyl Myristate, undiluted and diluted with corn oil or propylene glycol, was nontoxic when fed to rats. The acute oral LD_{50} for Myristyl Myristate was more than 14.4 g/kg in rats; for Cetyl Palmitate, more

Table 1. Frequency of use of Cetyl Esters

Product category	No. of formulations in category	No. containing ingredient
Eyebrow pencil	100	1
Eye shadow	597	3
Mascara	211	1
Other eye makeup preparation	130	4
Hair conditioner	693	8
Hair straighteners	59	1
Other hair preparations	382	2
Hair dyes and colors (all types)	1497	15
Blushers (all types)	283	2
Foundations	333	25
Lipstick	997	26
Makeup bases	159	7
Makeup fixatives	11	4
Other makeup preparations	155	11
Nail creams and lotions	18	1
Bath soaps and detergents	339	2
Deodorants (underarm)	293	5
Other personal cleanliness	317	2
Other shaving preparations	60	1
Cleansing	771	10
Face and neck	261	6
Body and hand	987	21
Moisturizing	873	31
Night	220	5
Paste masks (mud packs)	276	4
Other skin care preparations	782	6
Suntan gels, creams, liquids	196	4
Other suntan preparations	62	2
1995 Totals		***210***

Source. FDA, 1995.

than 14.4 g/kg in rats; and for Myristyl Stearate, more than 10 g/kg in mice, when diluted in corn oil (Elder, 1982a, 1982b, 1985).

Dermal

Myristyl Myristate, in studies using rabbits, had no dermal toxicity (dose 2.0 g/kg; Elder, 1982a).

A 50% slurry of Cetyl Palmitate in distilled water was not dermally toxic to rabbits when applied in a single 24-h occlusive patch at a dose of 2.0 g/kg. Slight irritation was noted (Elder, 1982b).

Irritation

Dermal

A trade product containing 60% to 65% Cetyl Esters was applied in a 0.5-g dose to intact and abraded skin of three albino rabbits. The sites were covered for 24 h. Scoring was done at the time of patch removal and 48 h later. The primary irritation index (PII) was 0 (Leberco Laboratories, 1971b).

A 50% dilution in oil (type unspecified) of Cetyl Palmitate applied twice daily for 5 days to five hairless mice was nonirritating (Henkel Department of Toxicology, 1974). Similarly, a 50% dilution applied in a 24-h patch exposure was nonirritating to rabbits (number not reported; Henkel Department of Toxicology, 1974).

Ocular

The right conjunctival sac of each of three albino rabbits was instilled with 0.1 g of a trade product containing 60% to 65% Cetyl Esters. The left eye(s) served as control. Examinations were performed every 24 h for 4 days, and then at day 7. No irritation was observed (Leberco Laboratories, 1971c).

In seven studies, Myristyl Myristate caused minimal to mild skin irritation and minimal eye irritation (Elder, 1982a).

Four separate studies tested the irritancy of Cetyl Palmitate using the Draize primary skin irritation technique. Occlusive patches were applied for 24 h. Reactions were evaluated at 24 h and 72 h readings and the PII scores were calculated as an average of the two readings. The maximum possible PII score was 8. The PIIs were as follows: 0.5 mL of a 5% w/w dispersion, score 0.38 (0.0 at 72 h); 0.5-g effective dosage, score 0; 0.5 g, score 0.17; and 0.5 mL, score 0.4 (0.0 at 72 h). Two additional irritation studies tested formulations containing 2.5% and 2.7% Cetyl Palmitate and had PIIs of 1.0 and 0.9, respectively. In four studies using the Draize eye irritation technique, Cetyl Palmitate was minimally irritating (Elder, 1982b).

Undiluted Myristyl Stearate had PII scores of 0.0 in rabbits after a 24-h occlusive patch exposure. Undiluted Myristyl Stearate caused slight, transient ocular irritation in rabbits (24-h Draize scores of 2, 4, and 6 out of a maximum of 110; no irritation was observed at later evaluations; Elder, 1985).

Sensitization

In guinea pig sensitization studies, Myristyl Myristate produced no evidence of skin sensitization (Elder, 1982a).

A 1% suspension of Cetyl Palmitate was minimally irritating but did not appear to be a sensitizing agent in guinea pigs (Elder, 1982b).

CLINICAL ASSESSMENT OF SAFETY

Five volunteers were patch-tested with a 50% dilution of Cetyl Palmitate in oil (type unspecified). Cetyl Palmitate was considered a nonirritant (Henkel Department of Toxicology, 1974). Details were not reported.

A formulation containing 8% Myristyl Myristate was minimally irritating in a human primary skin irritation study. The same product produced no evidence of sensitization in a human skin sensitization study (Elder, 1982a).

Various clinical studies were performed using trade products containing 2.5% or 2.7% Cetyl Palmitate. There was no evidence of primary irritation. Cetyl Palmitate was considered to be a "weak potential sensitizer." There were no cases of phototoxicity when the 2.7% formulation was tested using 10 normal subjects, and it was considered to have "low potential for photo-contact allergenicity" when tested using 25 normal subjects. A safety-in-use study tested the 2.5% formulation using 30 women; no irritation was noted. In a larger-scale study using 150 women and the 2.7% formulation, it was concluded that the formulation had a low potential for irritation (Elder, 1982b).

Results of clinical studies indicate that the Stearates and cosmetic products containing Stearates are essentially nonsensitizing; nonphototoxic; nonphotosensitizing; and, at most, minimal or mild skin irritants. The highest concentrations of Cetyl Stearate and Myristyl Stearate tested in the various studies were 50% and 9.8%, respectively (Elder, 1985). (Note: Photosensitization and phototoxicity studies were not conducted on these two stearates.)

SUMMARY

The mixture Cetyl Esters is a synthetic wax composed of a combination of the following six esters: Cetyl Palmitate, Cetyl Stearate, Myristyl Myristate, Myristyl Stearate, Cetyl Myristate, and Stearyl Stearate. The CIR Expert Panel had previously conducted safety assessments on the first four ingredients.

Cetyl Esters is used in cosmetic formulations as a skin-conditioning agent–emollient.

The oral LD_{50} (mice) of a product containing 60% to 65% Cetyl Esters was more than 20 g/kg; for Myristyl Myristate, more than 14.4 g/kg (rats); for Cetyl Palmitate, more than 5 g/kg (rats); and for Myristyl Stearate, more than 10 g/kg (mice).

In acute dermal studies, 2.0 g/kg Myristyl Myristate was nontoxic to rabbits. Slight irritation was noted when 2.0 g/kg Cetyl Palmitate was applied in a 24-h patch.

No irritation was noted with 0.5 g of a formulation containing 60% to 65% Cetyl Esters was applied to intact and abraded rabbit skin. The same formulation was not an ocular irritant for rabbit eyes. Myristyl Myristate caused mild skin irritation and minimal eye irritation. Cetyl Palmitate was not a dermal irritant and was minimally irritating for rabbit eyes. Myristyl Stearate was nonirritating to rabbit skin after a 24-h occlusive patch exposure, and was a slight, transient ocular irritant.

No evidence of sensitization was found when Myristyl Myristate was tested; Cetyl Palmitate caused minimal irritation but no sensitization.

In clinical dermal studies, 50% Cetyl Palmitate was found to be nonirritating. Other studies found a formulation containing 2.7% Cetyl Palmitate to be a weak potential sensitizer and a low potential irritant. There were no instances of phototoxicity. A formulation containing 8% Myristyl Myristate was minimally irritating but not sensitizing. Stearates of varying concentrations were essentially nonsensitizing, nonphototoxic, and nonphotosensitizing, and were minimal to mild skin irritants.

DISCUSSION

The CIR Expert Panel used data from four previously reviewed esters of fatty acids and fatty alcohols, and their structural similarity to the Cetyl Esters is evidence to suggest that the Cetyl Esters mixture is safe as used in cosmetics.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that Cetyl Esters is safe as used in cosmetics.

REFERENCES

Cosmetic, Toiletry and Fragrance Association (CTFA). 1995. Use Levels for Various Ingredients. Unpublished data submitted by CTFA.*

Elder R., ed. 1982a. Final report on the safety assessment of myristyl myristate and Isopropyl myristate. *J. Am. Coll. Toxicol.* 1(4):55–80.

Elder R., ed. 1982b. Final report on the safety assessment of octyl palmitate, cetyl palmitate and isopropyl palmitate. *J. Am. Coll. Toxicol.* 1(2):13–35.

Elder R., ed. 1985. Final report on the safety assessment of butyl stearate, cetyl stearate, isobutyl stearate, isocetyl stearate, isopropyl stearate, myristyl stearate, and octyl stearate. *J. Am. Coll. Toxicol.* 4(5):107–146.

Food and Drug Administration (FDA). 1992. Modification in Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Composition Statements. *Federal Register* 57:3128–3130.

FDA. 1995. Frequency of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

Henkel Department Of Toxicology. 1974. Cutina CP/Cetyl Palmitate/ Toxicological Data. Report No. 740038. Unpublished data submitted by Henkel KgaA.*

Leberco Laboratories. 1971a. LD_{50} of Cetina No. 718 in mice. Assay #: 16865. Unpublished data submitted by CTFA.*

Leberco Laboratories. 1971b. Primary irritation of Cetina No. 718 in mice. Assay #: 16866. Unpublished data submitted by CTFA.*

Leberco Laboratories. 1971c. Ocular irritation of Cetina No. 718 in mice. Assay #: 16867. Unpublished data submitted by CTFA.*

National Formulary. 1990. *The United States Pharmacopeia.* Rockville, MD: US Pharmacopeial Convention.

Nikitakis J. M., and McEwen G. N., Jr. eds. 1990. *CTFA Compendium of Cosmetic Ingredient Composition—Descriptions I.* Washington, DC: CTFA.

Wenninger J. A, and McEwen G. N., Jr. eds. 1995a. *International Cosmetic Ingredient Dictionary,* 6th ed. Washington, DC: CTFA.

Wenninger J. A, and McEwen G. N., Jr. eds. 1995b. *International Cosmetic Ingredient Handbook,* 3rd ed. Washington, DC: CTFA.

*Available for review: Director, Cosmetic Ingrediant Review, 1101 17th Street, NW, Washington, DC 20036.