Final Report on the Safety Assessment of Ceteareth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -20, -22, -23, -24, -25, -27, -28, -29, -30, -33, -34, -40, -50, -55, -60, -80, and -100[1]

Ceteareths, used in a large number of cosmetics as surfactants, are the polyethylene glycol (PEG) ethers of Cetearyl Alcohol (q.v.). To supplement the limited available data on Ceteareths, previous findings from the safety assessment of Polyethylene Glycol (PEG), several fatty alcohols (Cetearyl Alcohol, Cetyl Alcohol, and Stearyl Alcohol), and Steareths were considered. These data indicate little evidence of toxicity. Although various metabolites of monoalkyl ethers of ethylene glycol are reproductive and developmental toxins, given the methods of manufacture of Ceteareth compounds, there is no likelihood of such compounds being present as impurities. Further, there would be only limited ethylene glycol monomer linked by an ether group to the Ceteareth moiety for the PEG-5 compounds, little for the PEG-10 compounds, and virtually none for the PEG-20 and higher compounds. Even if linked to ethylene glycol monomer, it was considered unlikely that the Ceteareth moieties would be metabolized (e.g., via β-oxidation) to simple methyl, ethyl, propyl, or butyl alkyl groups. As the current data indicate, such short alkyl chains are needed in order for the production of toxic alcohol or aldehyde dehydrogenase metabolites. For longer alkyl chains there is evidence of diminishing toxicity, and extrapolation to much longer chains such as expected in the Ceteareth moieties suggests that there is no reproductive or developmental hazard posed by these Ceteareth compounds. The principal clinical finding related to PEGs is based on data in bum patients—PEGs were mild irritants/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. In the absence of specific impurities data, the possible presence of 1,4-dioxane and ethylene oxide impurities was of concern. The importance of using the necessary purification procedures to remove these impurities was stressed. Creams containing Ceteareth-20 enhanced drug absorption. Ceteareth-15 (10% in formulation) was minimally irritating to rabbits after a single dermal exposure. In ocular studies, ethoxylated Cetearyl Alcohol solution was a severe irritant to unrinsed rabbit eyes and moderately irritating to rinsed eyes. In clinical studies, Ceteareth-15 (1.5% in formulation) produced minimal irritation when tested in both a 4- and 21-day patch test, and was not a sensitizer when tested (1.35% in formulation) in a repeat-insult patch test. Based on the limited data on Ceteareths and the extensive data on chemically related ingredients, it was concluded that these ingredients are safe as used in cosmetic formulations. These ingredients, however, should not be used on damaged skin.

INTRODUCTION

Ceteareths are the Polyethylene Glycol (PEG) ethers of Cetearyl Alcohol (q.v.). 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:

> Cetearyl Alcohol (is) safe as (a) cosmetic ingredient in the present practices of use (Elder 1988a).
>
> 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).

Cetearyl Alcohol is comprised of Cetyl Alcohol and Stearyl Alcohol. These ingredients also have been reviewed previously by the CIR Expert Panel with the following conclusions:

> Cetyl Alcohol (is) safe as (a) cosmetic ingredient in the present practices of use (Elder 1988a).
>
> Stearyl Alcohol is safe as currently used in cosmetics (Elder 1985).

Further, Ceteareths are chemically similar to Steareths (which are derived from stearyl alcohol). Steareths also have been reviewed previously by the CIR Expert Panel with the following conclusions:

> Steareth-2, -4, -6, -7, -10, -11, -13, -15, and -20 are safe as cosmetic ingredients in the present practices of use and concentrations (Elder 1988b).

Because there are limited data specifically on the Ceteareth family, the relevant data from the Final Reports on each of the above ingredients have been extracted and summarized in this review as a part of the basis for the assessment of safety of Ceteareths. Summaries of studies contained in these earlier reviews *appear in italicized font.*

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CHEMISTRY

Definition and Structure

Ceteareths -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -20, -22, -23, -24, -25, -27, -28, -29, -30, -33, -34, -40, -50, -55, -60, -80, and -100 (CAS No. 68439-49-6 [generic]) are the polyethylene glycol ethers of Cetearyl Alcohol that conform to the formula, $R(OCH_2CH_2)_nOH$ (Wenninger and McEwen 1997). The R group in the formula represents a blend of alkyl groups derived from cetyl and stearyl alcohol. The average number of ethylene glycol ether monomers in the polymer (n in the above formula) is expressed as the number in each named Ceteareth, e.g., Ceteareth-2. Ceteareths are identified in Japan as polyoxyethylene cetyl/stearyl ether (Rempe and Santucci 1992).

Chemical and Physical Properties

The properties of Ceteareths are dependent on the degree of polymerization of the polyethylene glycol (hydrophilic) segment. They can be liquids to waxy solids. Compounds with 1 to 5 moles ethylene oxide are soluble in oil and many hydrocarbons. Water solubility increases with increasing ethylene oxide content (Budavari 1989).

Method of Manufacture

Ceteareths (as well as other polyoxyethylene alcohols) are nonionic surfactants prepared by ethoxylation of fatty alcohol mixtures with ethylene oxide (Budavari 1989).

Impurities

Technical grade Cetearyl Alcohol contains 65–80% stearyl and 20–35% cetyl alcohols. Other alcohols with varying chain lengths are found in small amounts. The following impurities have been reported for Cetearyl Alcohol mixtures: hydrocarbons (consisting mostly of n-*hexadecane and* n-*octadecane), 0.1–1.4%; odd-numbered straight-chain alcohols, 1–3.5%; branched-chain primary alcohols, 0.2–2%. Even-numbered straight-chain alcohols (C_8–C_{22}) comprise 90–95% of the mixture (Elder 1988a). Silverstein et al. (1984) reported that PEG-6 can contain small amounts of monomer and dimers, but the amounts were not quantified. Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger et al. 1975). The amount of peroxide in PEGs 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 PEGs, 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 can 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). In the CIR safety assessment of the PEG-Stearates, the cosmetic industry reported that it is aware that 1,4-dioxane can be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations (Elder 1983).

USE

Cosmetic

Ceteareths function in cosmetics as surfactants; Ceteareths -2 to -18 are used as emulsifying agents, Ceteareths -20 to -40 are used as solubilizing agents and cleansing agents (except for Ceteareth-22 which is used as an emulsifying agent and viscosity decreasing agent), and Ceteareths -50 to -100 are used as cleansing agents (Wenninger and McEwen 1997). The product formulation data submitted to the Food and Drug Administration (FDA) in January 1996 reported that these ingredients were collectively used in 680 cosmetic formulations (Table 1) (FDA 1996). There were no reported uses for many Ceteareths.

The concentrations at which these ingredients are used are not known because concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). However, data provided earlier to the FDA (1984) indicated that the highest concentration of use was 50%. Maximum concentrations reported for individual ceteareths include: Ceteareth-3 at 5%, Ceteareth-5 at 10%, Ceteareth-6 at 25%, Ceteareth-10 at 5%, and Ceteareth-12 at 50%, Ceteareth-15 at 5%, Ceteareth-17 at 5%, and Ceteareth-20 at 10% (FDA 1984). Recent information supplied from one company indicated use of Ceteareth-15 at 1.35% in facial cleansers, 2.0% in shampoos, 3.5% in cuticle conditioners, and 10% in hair dressing formulations (CTFA 1996).

International

Ceteareths are listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) and must conform to the specifications of the *Japanese Cosmetic Ingredient Codex* (Yakuji Nippo, Ltd. 1994). They can be used without restrictions in all CLS categories except eyeliners, lipsticks and lip creams, and dentifrices.

BIOLOGY

Absorption, Metabolism, and Distribution

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the more solid the PEG compound, the less absorption that occurs. In both oral and i.v. studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human burn patients, monomeric ethylene glycol was

TABLE 1
Frequency of use of Ceteareths (FDA 1996)

Product category	No. formulations in category	No. containing listed Ceteareth
Ceteareth-3		
Other skin care preparations	810	1
1996 total for Ceteareth-3		**1**
Ceteareth-5		
Eyeliner	533	1
Hair conditioners	715	4
Tonics, dressings, and other hair grooming aids	604	3
Hair dyes and colors	1612	1
Cleansing (creams/lotions/powders/sprays)	820	1
Body and hand skin care preparations (excluding shaving)	1012	5
Moisturizing skin care (creams/lotions/powders/sprays)	942	3
Suntan gels, creams, and liquids	196	2
1996 total for Ceteareth-5		**20**
Ceteareth-6		
Eyeliner	533	1
Dentifrices	47	2
Cleansing (creams/lotions/powders/sprays)	820	2
Paste masks (mud packs)	300	2
Other skin care preparations	810	1
Indoor tanning preparations	67	1
1996 total for Ceteareth-6		**9**
Ceteareth-10		
Hair dyes and colors	715	21
Hair bleaches	113	5
Other manicuring preparations	83	1
Body and hand skin care preparations (excluding shaving)	1012	1
Other skin care preparations	810	1
1996 total for Ceteareth-10		**29**
Ceteareth-12		
Hair conditioners	715	1
Shampoos (noncoloring)	972	1
Foundations	355	2
Aftershave lotion	268	1
Cleansing (creams/lotions/powders/sprays)	820	10
Face and neck skin care preparations (excluding shaving)	300	5
Body and hand skin care preparations (excluding shaving)	1012	13
Foot powders and sprays	33	1
Moisturizing skin care (creams/lotions/powders/sprays)	942	4
Night skin care (creams/lotions/powders/sprays)	226	5
Paste masks (mud packs)	300	2
Other skin care preparations	810	8
Suntan gels, creams, and liquids	196	2
Indoor tanning preparations	67	1
Other suntan preparations	68	1
1996 total for Ceteareth-12		**57**

(Continued on next page)

TABLE 1
Frequency of use of Ceteareths (FDA 1996) *(Continued)*

Product category	No. formulations in category	No. containing listed Ceteareth
Ceteareth-15		
Hair conditioners	715	1
Hair dyes and colors	1612	8
Face and neck skin care preparations (excluding shaving)	300	1
Indoor tanning	67	1
1996 total for Ceteareth-15		**11**
Ceteareth-20		
Baby lotions, oils, powders, and creams	64	1
Bubble baths	211	1
Eyebrow pencil	99	1
Eye lotion	22	1
Mascara	218	1
Other eye makeup preparations	136	2
Other fragrance preparations	195	2
Hair conditioners	715	108
Hair straighteners	50	3
Permanent waves	434	2
Rinses (noncoloring)	60	5
Shampoos (noncoloring)	972	5
Tonics, dressings, and other hair grooming aids	604	2
Wave sets	95	1
Other hair preparations	395	10
Hair dyes and colors	1612	74
Hair tints	57	25
Hair lighteners with color	9	3
Hair bleaches	113	1
Other hair coloring preparations	71	9
Foundations	355	2
Makeup bases	154	2
Other makeup preparations	157	1
Bath soaps and detergents	372	1
Other personal cleanliness products	339	1
Aftershave lotion	268	3
Cleansing (creams/lotions/powders/sprays)	820	30
Depilatories	53	8
Face and neck skin care preparations (excluding shaving)	300	16
Body and hand skin care preparations (excluding shaving)	1012	49
Foot powders and sprays	33	1
Moisturizing skin care (creams/lotions/powders/sprays)	942	29
Night skin care (creams/lotions/powders/sprays)	226	5
Paste masks (mud packs)	300	9
Other skin care preparations	810	24
Suntan gels, creams, and liquids	196	9
Indoor tanning preparations	67	2
Other suntan preparations	68	3
1996 total for Ceteareth-20		**452**

TABLE 1
Frequency of use of Ceteareths (FDA 1996) *(Continued)*

Product category	No. formulations in category	No. containing listed Ceteareth
Ceteareth-25		
Tonics, dressings, and other hair grooming aids	604	2
Hair tints	57	30
Indoor tanning preparations	67	1
1996 total for Ceteareth-25		**33**
Ceteareth-30		
Eyeliner	533	1
Hair conditioners	715	5
Hair dyes and colors	1612	3
Other hair coloring preparations	71	5
Deodorants (underarm)	303	1
Aftershave lotion	268	1
Cleansing (creams/lotions/powders/sprays)	820	1
Depilatories	53	1
Face and neck skin care preparations (excluding shaving)	300	1
Body and hand skin care preparations (excluding shaving)	1012	1
Moisturizing skin care (creams/lotions/powders/sprays)	942	1
Other skin care preparations	810	1
Indoor tanning preparations	67	4
1996 total for Ceteareth-30		**26**
Ceteareth-33		
Hair conditioners	715	3
Tonics, dressings, and other hair grooming aids	604	1
Cleansing (creams/lotions/powders/sprays)	820	1
1996 total for Ceteareth-33		**5**
Ceteareth-100		
Hair dyes and colors	715	37
1996 total for Ceteareth-100		**37**

isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

Three creams containing 2, 3, and 5% *w/w* Ceteareth-20 were tested as possible vehicles for dermal delivery of the analgesic piketoprofen. The 2% (*w/w*) Ceteareth-20 cream also contained 1.8% piketoprofen, 3% polyoxyethylene sorbitan monolaurate, 2% sorbitan monolaurate, 24.9% long-chain alcohols mixture, and 66.3% water. The cream with 3% Ceteareth-20 also contained 1.8% piketoprofen, 30.2% long-chain alcohols mixture, and 65% water. The cream with 5% Ceteareth-20 also contained 1.8% piketoprofen and 93.2% long-chain alcohols mixture. The creams were applied to the clipped skin of albino rabbits (numbers not stated) such that 200 mg of the analgesic/kg body weight was applied. The formulation was left in contact with the skin for 72 hours. Blood samples were taken from the marginal ear vein prior to product application and at hourly intervals thereafter. The samples were analyzed by thin-layer chromatography for 4-biphenylacetate (BPA) content which is a metabolite of the analgesic. All three creams containing Ceteareth-20 enhanced absorption of the drug as compared to three creams which did not contain Ceteareths. The most effective penetration was achieved with the 2% Ceteareth-20 cream (which also contained other surfactants). Although comparable (though less) penetration was also reached with another cream that contained surfactants other than Ceteareth-20, the narrow time base of the blood level curve indicated loss of drug to capillary blood and, hence, elimination from the site of action. The 2% Ceteareth-20 cream offered rapid penetration as well as retention in the subcutaneous tissue such that the drug appeared in circulating blood. High plasma levels of the metabolite were noted with the 2% Ceteareth-20 cream and were attributed to rapid skin penetration via the pilosebaceous glands. It was suggested that the lower penetration values for the 3 and 5% Ceteareth-20 creams were "due to lowering of the thermodynamic activity of piketoprofen by micellar trappings of the active compound or by interactions with the skin." Thus, when a combination of surfactants was used, "the release rate of piketoprofen from the organic phase was increased by the formation of high activity coefficient surfactant-drug complexes" (Fabregas et al. 1986).

ANIMAL TOXICOLOGY

Toxicity

The oral LD_{50} of cetyl alcohol was >8.2 g/kg for rats. The animals in this study had signs of central nervous system depression and labored respiration. With formulations containing 2.0–4.0% cetyl alcohol, no significant toxic effects were observed in either acute oral or dermal studies. In a subchronic dermal toxicity study, 30.0% cetyl alcohol caused dermal infiltrates of histiocytes in rabbits. Similar experiments with formulations containing 11.5% cetyl alcohol reported exfoliative dermatitis, parakeratosis, and hyperkeratosis to the skin of rabbits. A formulation containing 2.0% cetyl alcohol caused only mild inflammation. A single 6-hour inhalation exposure to cetyl alcohol vapor (26 ppm) by mice, rats, and guinea pigs caused slight irritation of the mucous membranes of the eyes, nose, throat, and respiratory passages. There were no signs of systemic toxicity, and no deaths were reported. However, 10-minute exposures of 9.6 mg/L every 30 minutes for 4 hours produced no treatment-related changes in rats and guinea pigs. A 6-hour exposure to a cetyl alcohol concentration of 2220 mg/m^3 resulted in death of all animals (Elder 1988a).

Stearyl Alcohol had an LD_{50} of >8 g/kg in rats (Elder 1985).

In a subchronic dermal study, Steareth-20 was nontoxic to rabbits when tested at 4% in formulation. The test material produced slight to moderate dermal irritation (but the response was less than irritation produced by the vehicle control) (Elder 1988b).

Toxicity studies with rats, rabbits, and dogs indicate that PEGs have low oral and dermal toxicity. In general, the greater molecular weight PEGs appear to be less toxic than the lighter PEGs in oral studies. Acute oral LD_{50}s for PEGs in rabbits were 17.3 g/kg (100% PEG-6) and 76 g/kg (100% PEG-75). In subchronic, 90-day oral toxicity studies involving groups of albino rats, the highest (PEG-20M) and lowest (PEG-6) molecular weight PEGs tested did not induce toxicity nor death when administered daily at concentrations of 4% or less; PEG-20M was administered in the diet and PEG-6 in drinking water. Toxic effects were also not observed in groups of dogs that received PEG-8, PEG-32, and PEG-75 at concentrations of 2% in the diet for 1 year. In acute dermal toxicity studies, no deaths were reported in groups of rabbits dosed with undiluted PEG-6 (20 ml/kg) or 40% PEG-20M (20 ml/kg). In other dermal toxicity studies, there was no evidence of toxicity in a group of rabbits that received daily applications of PEG-6 5 days per week (2 ml/kg/day) for 18 weeks, and none in rabbits that received daily applications of PEG-20M (0.8 g/kg/day) for 30 days; transient, mild erythema was observed in the 30-day study. The only evidence of systemic toxicity that resulted from dermal exposure was noted in rabbits that received repeated applications of an antimicrobial cream containing 63% PEG-6, 5% PEG-20, and 32% PEG-75 to excised skin *sites for 7 days. No adverse reproductive effects occurred during subchronic (90 days) and chronic (2 years) oral toxicity studies of PEG-6 to -32 and PEG-75. In the subchronic study, PEG-75 was tested at a dose of 0.23 g/kg/day. PEG-75 was tested at doses up to 0.062 g/kg/day and, PEG-6 to -32, at doses up to 1.69 g/kg/day in the chronic study (Andersen 1993).*

Dermal Irritation and Sensitization

Five 8-hour dermal exposures of a cream containing 3.0% cetearyl alcohol to intact and abraded skin were mildly irritating to six New Zealand albino rabbits. Mean erythema scores for intact skin ranged from 1.0 to 3.0 at 8 hour and from 1.17 to 2.67 at 24 hours post application (Elder 1988a).

Formulations containing cetyl alcohol caused no irritation to the skin of rabbits in some studies but induced well-defined erythema in others. There was no correlation between the concentration of cetyl alcohol and these effects, which indicated responses to the formulations themselves rather than to this particular ingredient (Elder 1988a).

A 3-month study testing 8% Stearyl Alcohol (in formulation) in rabbits found slight to well-defined erythema and desquamation; at necropsy, mild inflammation was at the application site. Undiluted Stearyl Alcohol produced mild dermal irritation in rabbits following a 24-hour exposure. Stearyl Alcohol, 24% in formulation, did not induce contact sensitization in guinea pigs. Stearyl Alcohol was negative in a rabbit ear comedogenicity study (Elder 1985).

Steareth-2 and -10 were at most mild irritants to rabbit skin when tested in formulation and at concentrations of up to 60% in water. Steareth-20 was a mild dermal irritant to rabbits in a 60% aqueous solution, and a moderate irritant when tested in formulation (Elder 1988b).

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).

Ceteareth-15 (10% in a hair dressing formulation) was applied in a single-insult occlusive patch to six rabbits. At the 24 hours observation five rabbits had erythema scores of 2; the sixth rabbit had a score of 1. Edema scores of 2 and 1 were noted in four and two rabbits, respectively. By 72 hours the reactions had reduced in four rabbits and remained unchanged in the other two (one with erythema and edema scores of 1 and 1, and the other with scores of 2 and 2). The Primary Irritation Index (PII) for the group was 1.50 (maximum score 8) and the test material was considered minimally irritating (CTFA 1975).

Ocular Irritation

There was no evidence of ocular irritation produced by a cream containing 3.0% cetearyl alcohol when instilled into one eye of each of nine albino rabbits (Elder 1988a).

Undiluted cetyl alcohol and most product formulations containing cetyl alcohol were nonirritating to the eyes of rabbits,

but a few cases of transient conjunctival redness and hyperemia were reported (Elder 1988a).

In an ocular irritation study, undiluted stearyl alcohol produced reactions graded 5 (maximum 110); reactions cleared by day 4 (Elder 1985).

Steareth-2 and -10, at concentrations of up to 60% in water, were at most mildly and minimally irritating, respectively, to rabbit eyes. Steareth-20 was a moderate ocular irritant in, rabbits at an unspecified concentration (Elder 1988b).

PEGs -6 and -75 did not cause corneal injuries when instilled (undiluted, 0.5 ml) into the eyes 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).

In each of two modified ocular irritation studies, 0.1 ml of an ethoxylated cetearyl alcohol solution (concentration not reported; pH of solution was 6.5) was instilled into the conjunctival sac of one eye of each of nine rabbits. Three of the treated eyes were subsequently rinsed. Evaluations were made at 24, 48, and 72 hours and at 4 and 7 days after instillation. The Draize scale was used in which the maximum score is 110. In one study, the material was a severe irritant to unrinsed eyes and a moderate irritant to rinsed eyes. In the second study, the test material was extremely irritating to unrinsed eyes and mildly irritating to rinsed eyes (Product Safety Labs 1980a; b).

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). 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 Ceteareth compounds, the Panel concluded there is no likelihood of methoxyethanol, ethoxyethanol, etc., being present as an impurity. Further, the Expert Panel concluded that there would only be limited ethylene glycol monomer linked by an ether group to the Ceteareth moiety for the PEG-5 compounds, little for the PEG-10 compounds, and virtually none for the PEG-20 and higher compounds. Even if linked to ethylene glycol monomer, the Panel concluded that it was unlikely that the Ceteareth moieties would be metabolized (e.g., via β-oxidation) to simple methyl, ethyl, propyl, or butyl alkyl groups. As the current data indicate, such short alkyl chains are needed in order for the production of toxic alcohol or aldehyde dehydrogenase metabolites. For longer alkyl chains there is evidence of diminishing toxicity, and extrapolation to much longer chains such as expected in the Ceteareth moieties suggested to the Expert Panel that there is no reproductive or developmental hazard posed by these Ceteareth compounds.

MUTAGENICITY

Cetyl alcohol (dose not specified) was not mutagenic in Salmonella typhimurium *LT2 mutant strains in the spot test (Elder 1988a).*

Stearyl Alcohol was not mutagenic in the Ames assay, either with or without metabolic activation (Elder 1985).

The review on Steareths reported that an unspecified alcohol ethoxylate did not induce chromosomal anomalies in either hamster bone marrow cells (following oral dosing of the hamsters) or in human leukocytes (which had been incubated with the test agent). The test agent was also nonmutagenic in the dominant lethal assay (male mice) (Elder 1988b).

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-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/L (Andersen 1993).

CARCINOGENICITY

Stearly Alcohol did not promote tumor formation in mice when tested with 7,12-dimethybenz[a]anthracene DMBA (Elder 1985).

The review on Steareths reported that a structurally undefined polyoxyethylene alkyl ether was neither a carcinogen nor a tumor promotor in a mouse skin-painting study (Elder 1988b).

All of the carcinogenicity data available on the PEGs *was 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—rats; 1 year of dosing—mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).*

CLINICAL STUDIES

Dermal Irritation and Sensitization

No skin sensitization was observed in 25 panelists who had been inducted and challenged with a cream containing 3.0% cetearyl alcohol. In skin irritation and sensitization studies, product formulations containing up to 8.4% cetyl alcohol produced no substantial evidence of irritation or sensitization. A 30% concentration of cetyl alcohol in petrolatum caused sensitization reactions in 11.2% of 330 subjects in a sensitization study. However, no positive sensitization reactions were observed with

studies of formulations containing up to 5.0% cetyl alcohol. Photosensitization studies of products containing 1.0% and 4.0% cetyl alcohol were negative (Elder 1988a).

Results of screening patch testing of large populations indicated a contact sensitization rate of 0.51% for Stearyl Alcohol (19 of 3740 sensitized) (Elder 1985).

Steareth-2, 60% in water, was not a primary irritant or a sensitizer to human skin. Steareth-2, 0.6% in a mousse, was a mild irritant. A body lotion containing 2.75% Steareth-2 and 2.25% Steareth-20 was not phototoxic. At a concentration of 60% in water, Steareth-10 was not an irritant, and Steareth-20 (also tested in formulation) was neither an irritant, sensitizer, nor phototoxic to human skin (Elder 1988b).

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 hours 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 lotion containing 1.5% Ceteareth-15 was tested in a 21-day cumulative irritancy test using 11 panelists. Patches were applied to the backs of panelists who were instructed to remove them after 23 hours and bathe or shower immediately thereafter. Sites were scored daily prior to application of the subsequent patch. Minimal erythema was noted after the 19th patch in one panelist but was not noted again. The test material was considered to be essentially nonirritating (Hill Top Research 1975).

A cleansing lotion containing 1.5% Ceteareth-15 was tested in a 4-day minicumulative irritancy test using 19 panelists. Summary results indicated that no reactions were noted in seven panelists, reactions scored as ± (the first nonzero score) were noted in nine panelists, and reactions scored as 1 (second nonzero score) were noted in three. The PII was 0.39 (maximum score 47.5) (Hill Top Research Inc. 1988).

A repeat-insult patch test (RIPT) of a formulation containing 1.35% Ceteareth-15 was performed using 98 panelists (77 females, 21 males). During induction, 24-hour patches containing the test material were applied to the back for a total of nine exposures. Sites were evaluated prior to application of the subsequent patch. Challenge occurred after a 2-week nontreatment period. Faint erythema was noted in 14 panelists during induction. Nine of these panelists had only a single incidence of reaction. No reactions were noted to challenge (Hill Top Research, Inc. 1989).

DISCUSSION FROM PREVIOUS REPORTS

Although there was no discussion section in the report on stearyl alcohol, the ingredient was characterized as having benign biological activity (Elder 1985).

The discussion section in the Steareths report explained that based on chemical similarity, the Panel would be using the data on Steareths -2, -10, and -20 to support the safety of other Steareths (-4, -6, -11, -13, and -15). Further, the negative mutagenicity studies on an alcohol ethoxylate of unspecified chain length precluded the need for mutagenicity testing specifically on Steareths (Elder 1988b).

In its review of cetearyl alcohol and cetyl alcohol, the Expert Panel concluded that these ingredients were safe for use as cosmetic ingredients. They noted that, in general, long-chain aliphatic alcohols induced minimal ocular and skin irritation but not sensitization or comedogenicity in rabbits. Clinical studies also indicated a low order of skin irritation and sensitization. The Panel also noted that because there was little information on the subchronic and chronic toxicities and genotoxicity of long-chain aliphatic alcohols, they relied on previous assessments they conducted on fatty acids and long-chain aliphatic esters. The close structural similarities of these compounds to the long-chain aliphatic alcohols suggest that the latter ingredients will have similar biological activities (Elder 1988a).

In its review of the PEG family, the CIR Expert Panel was concerned about the evidence of sensitization and nephrotoxicity in burn patients treated with a PEG-based antimicrobial cream. PEG was determined to be the cause of these responses in both animal and human studies. However, there was no evidence of systemic toxicity or sensitization in studies with intact skin. Because of this, the Expert Panel qualified their conclusion on the safety of the PEGs to state that cosmetic formulations containing PEGs should not be used on damaged skin. Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetic industry should continue to use the necessary purification procedures to remove these impurities from the ingredient before blending it into cosmetic formulations (Andersen 1993).

SUMMARY

Ceteareths, used in cosmetics as surfactants, are the polyethylene glycol (PEG) ethers of Cetearyl Alcohol (q.v.). In addition to limited safety test data on Ceteareths, the report summarizes findings from the CIR reports on PEGs, Cetearyl Alcohol, Cetyl Alcohol, Stearyl Alcohol, and Steareths.

Ceteareths were used in a total of 680 formulations in 1996. Data from 1984 indicated use at up to 50% (Ceteareth-12); recent data from one company indicated that Ceteareth-15 was used up to 10% (5% had been the maximum concentration reported in 1984).

Creams containing Ceteareth-20 enhanced drug absorption. Ceteareth-15 (10% in formulation) was minimally irritating to rabbits after a single dermal exposure. In ocular studies, ethoxylated Cetearyl Alcohol solution was a severe irritant to unrinsed rabbit eyes and moderately irritating to rinsed eyes.

In clinical studies, Ceteareth-15 (1.5% in formulation) produced minimal irritation when tested in both a 4- and 21-day patch test, and was not a sensitizer when tested (1.35% in formulation) in an RIPT.

DISCUSSION

In evaluating the safety of the Ceteareths, the CIR Expert Panel relied extensively on data from evaluations of chemically-related ingredients. Steareths, which are most chemically related to Ceteareths, had previously been reviewed as "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1988b). Although use data indicated that Steareths were used in formulations at ≤25%, the report included studies that tested the moieties at up to 60% in water with no adverse effects. Likewise, the CIR review of the components of Ceteareths, namely Polyethylene Glycol, Cetearyl Alcohol, Cetyl Alcohol, and Stearyl Alcohol, indicated these ingredients can be safely used in cosmetic formulations. The Panel was of the opinion that these data were sufficient to evaluate Ceteareths as "safe as used."

The Panel cautioned that Ceteareths, particularly Ceteareth-20, enhance drug absorption. Care should be taken when creating formulations, especially those products intended for use on infants.

As Ceteareths are polyoxyethylene glycol compounds, the Panel believed that stipulations made in their review of PEGs (Andersen 1993) should be maintained; that is to say that Ceteareths should not be used on damaged skin. Further, in the absence of impurities data, the Panel cautioned that a Ceteareth preparation should not contain 1,4-dioxane or ethylene oxide, which are possible oxidation products.

As described earlier in this report, the possibility of reproductive and developmental effects that could be associated with ethylene glycol and its ethers was assessed and determined not to be a concern.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that Ceteareth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -20, -22, -23, -24, -25, -27, -28, -29, -30, -33, -34, -40, -50, -55, -60, -80, and -100 are safe as used in cosmetic formulations. Ceteareths should not be used on damaged skin.

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