Final Report on the Safety Assessment of Ceteth-1, -2, -3, -4, -5, -6, -10, -12, -14, -15, -16, -20, -24, -25, -30, and -45[1]

The Ceteth family of ingredients are the polyethylene glycol (PEG) ethers of cetyl alcohol. They are manufactured by the ethoxylation of cetyl alcohol with the number of moles of ethylene oxide corresponding to the average polyethylene glycol chain length desired. Not all of the polymer chain lengths covered in this assessment are currently reported to be used, but all are listed as cosmetic ingredients and may have been used in the past and could be used in the future. Ceteths are surfactants used as emulsifying, cleansing, and solubilizing agents in cosmetic formulations. Limited safety test data are available on ingredients in the Ceteth family, all consistent with surfactant properties. In separate studies, 2.5% Ceteth-2 was irritating to abraded skin, but 3.0% was not irritating to intact skin. Dose-dependent irritation was noted for Ceteth-2 and Ceteth-10 at concentrations ranging from 5% to 100%. Ceteth-20 was found to enhance transposition of a marker from phage λ to bacterial DNA. Toxicity data, including reproductive and developmental toxicity, carcinogenesis data, and clinical testing data, available from previous safety assessments on Polyethylene Glycol and Cetyl Alcohol, were summarized. Although PEGs were mild irritants/sensitizers, there was evidence of nephrotoxicity in burn patients exposed to PEGs, and no such effects were seen in animal studies on intact skin. This led to a recommendation that PEGs not be used on damaged skin. Irritant effects of Ceteths on abraded skin not seen with intact skin likewise suggested that cosmetic manufacturers should not use Ceteths in products that may be used on damaged skin. Although metabolites of ethylene glycol monalkyl ethers are reproductive and developmental toxins, it was considered unlikely that the relevant metabolites would be found in or produced from the use of Ceteths in cosmetic formulations. Of concern was the possible presence of 1,4-dioxane and ethylene oxide impurities. The importance of using the necessary purification procedures to remove these impurities was stressed. Inhalation of Cetyl Alcohol at 26 ppm for 6 hours caused mucosal irritation, but shorter exposures at a concentration of 9.6 mg/L caused no irritation. Based on this data and with particle size and cosmetic use concentrations, Ceteths were considered to be safe for aerosolized use. Based in part on the limited data available on Ceteths included in the report and on the previous reviews of the two components found in Ceteths, it was concluded that Ceteth-1, -2, -3, -4, -5, -6, -10, -12, -14, -15, -16, -20, -24, -25, -30, and -45 are safe in the present practices of use.

Received 25 February 1999; accepted 12 May 1999.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Susan N. J. Pang, former Scientific Analyst and Writer, prepared this report. Address correspondence to Dr. F. Alan Andersen, Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

International Journal of Toxicology, 18(Suppl. 2):1–8, 1999

1091-5818/99 $12.00 + .00

This report reviews the safety of Ceteth-1, -2, -3, -4, -5, -6, -10, -12, -14, -15, -16, -20, -24, -25, -30, and -45, used in cosmetics as emulsifying, cleansing, and solubilizing agents. Chemically, these surfactants are the polyethylene glycol (PEG) ethers of cetyl alcohol. These two basic components have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and Final Reports have been published. The following conclusions were made:

> *PEG-6, -8, -32, -75, 150, -14M, and -20M* are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).
>
> *Cetyl Alcohol* is safe for use in cosmetics (Elder 1988).

Because there are limited data specifically on the Ceteth family, the relevant data from the Final Reports on the PEG family and cetyl alcohol have been extracted and summarized in this review as a basis for the assessment of safety of Ceteths 1–45. *Studies contained in these earlier reviews appear in an italicized font.*

CHEMISTRY

Definition and Structure

Ceteth-2, -3, -4, -5, -6, -10, -12, -14, -15, -16, -20, -24, -25, -30, and -45 (CAS No. 9004-95-9 [generic]) are the polyethylene glycol ethers of cetyl alcohol (q.v.) that conform to the formula shown in Figure 1, where n has an average value equal to the number in the name (Wenninger and McEwen 1997).

Ceteth-1 is the ethylene glycol ether of cetyl alcohol; in the above structure, n = 1 (Wenninger and McEwen 1997). Ceteths are identified in Japan as polyoxyethylene cetyl ethers (Rempe and Santucci 1992).

Chemical and Physical Properties

The Ceteth family has a broad range of properties depending on the degree of polymerization of the PEG segment. The physical forms of these ingredients range from liquids to waxy solids. Compounds with 1–5 moles of ethylene oxide are soluble in oil and in many hydrocarbons. Solubility in water increases with the content of ethylene oxide (Budavari 1989).

$$CH_3(CH_2)_{14}CH_2(OCH_2CH_2)_nOH$$

FIGURE 1
Chemical formula for Ceteths, where n has an average value equal to the number in the name (Wenninger and McEwen 1997).

Method of Manufacture

Ceteths are manufactured by the ethoxylation of cetyl alcohol with the ingredient's corresponding number of moles of ethylene oxide (Budavari 1989).

Impurities

Silverstein et al. (1984) reported that PEG-6 may contain small amounts of monomer and dimers. The amounts were not quantified.

Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger, Azaz, and Donbrow 1975). The amount of peroxide in 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 may also contain 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1.4-Dioxane is a known animal carcinogen (Kociba et al. 1974; Hoch-Ligeti, Argus, and Arcos 1970; Argus, Arcos, and Hoch-Ligeti 1965). In the CIR safety assessment of the PEG-Stearates, the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations (Elder 1983).

Peroxides were found in Ceteth-20. The peroxide formation rate, when expressed in terms of peroxide number, was inversely proportional to the concentration of Ceteth-20. However, in terms of absolute concentration of peroxides, peroxide content was proportional to PEG concentration (Hamburger, Azaz, and Donbrow 1975).

USE

Cosmetic

The Ceteths are surfactants used as emulsifying, cleansing, and solubilizing agents (Wenninger and McEwen 1997). Table 1

TABLE 1
Cosmetic product formulation data on Ceteths (FDA 1996)

Product category	Total no. formulations in category	Total no. of formulations containing ingredient
Ceteth-2		
Hair conditioners	715	19
Permanent waves	434	3
Tonics, dressings, and other hair grooming aids	604	1
Makeup bases	154	1
Cuticle softeners	26	2
Other personal cleanliness products	339	2
Other shaving preparations	63	1
Moisturizing preparations	942	1
Other skin care preparations	810	1
Indoor tanning preparations	67	2
1996 total for Ceteth-2		**33**
Ceteth-5		
Moisturizing preparations	942	2
1996 total for Ceteth-5		**2**
Ceteth-10		
Hair conditioners	715	4
Hair sprays (aerosol fixative)	334	1
Foundations	355	6
Night preparations	226	2
Skin fresheners	244	1
Indoor tanning preparations	67	2
1996 total for Ceteth-10		**17**
Ceteth-12		
Hair conditioners	715	2
Moisturizing preparations	942	1
1996 total for Ceteth-12		**3**
Ceteth-14		
Other personal cleanliness products	339	1
Cleansing preparations	820	1
1996 total for Ceteth-14		**2**
Ceteth-16		
Other bath preparations	166	1
Hair conditioners	715	1
Shampoos (noncoloring)	972	1
Tonics, dressings, and other hair grooming aids	604	5
Deodorants (underarm)	303	2
Other personal cleanliness products	339	2
Aftershave lotion	268	2

(Continued on next page)

TABLE 1
Cosmetic product formulation data on Ceteths (FDA 1996) *(Continued)*

Product category	Total no. formulations in category	Total No. of formulations containing ingredient
Ceteth-16 (cont.)		
Moisturizing	942	4
1996 total for Ceteth-16		**18**
Ceteth-20		
Baby lotions, oil, powders, and creams	64	1
Eye makeup remover	95	1
Mascara	218	5
Other eye makeup preparations	136	2
Hair conditioners	715	9
Hair sprays (aerosol fixatives)	334	1
Hair straighteners	50	3
Permanent waves	434	18
Rinses (noncoloring)	60	1
Tonics, dressings, and other hair grooming aids	604	5
Wave sets	95	8
Other hair preparations	395	1
Other hair coloring preparations	71	9
Deodorants (underarm)	303	1
Other personal cleanliness products	339	2
Aftershave lotion	268	2
Beard softeners	4	1
Shaving cream	158	5
Cleansing preparations	820	9
Depilatories	53	3
Face and neck (excluding shaving preparations)	300	2
Body and hand (excluding shaving preparations)	1012	6
Moisturizing preparations	942	6
Night preparations	226	4
Paste masks (mud packs)	300	1
Ceteth-20 (cont.)		
Skin fresheners	244	1
Other skin care preparations	810	7
1996 total for Ceteth-20		**114**
Ceteth-24		
Baby lotions, oils, powders, and creams	64	1
Bubble baths	211	2
Other eye makeup preparations	136	3
Other fragrance preparations	195	5
Hair conditioners	715	1
Hair dyes and colors	1612	20
Foundations	355	12
Lipstick	997	1
Other makeup preparations	157	1
Aftershave lotion	268	2
Cleansing preparations	820	1
Body and hand preparations (excluding shaving preparations)	1012	2
Moisturizing preparations	942	5
Night preparations	226	3
Paste masks (mud packs)	300	1
Skin fresheners	244	2
Other skin care preparations	810	2
Suntan gels, creams, and liquids	196	2
Other suntan preparations	68	1
1996 total for Ceteth-24		**67**
Ceteth-25		
Cleansing preparations	820	1
1996 total for Ceteth-25		**1**
Ceteth-30		
Hair conditioners	715	2
1996 total for Ceteth-30		**2**

shows the product formulation data submitted to the Food and Drug Administration (FDA) in January 1996. These ingredients collectively were reported to be used in 259 cosmetic formulations (FDA 1996). Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). However, data provided to the FDA in 1984 indicated that the greatest concentration used was 25% Ceteth-20 in one hair straightener (FDA 1984). More recent data submitted directly by CTFA indicated the following maximum concentration of use for certain formulations: Ceteth-2 and Ceteth-16 at 5% (hair conditioners), Ceteth-10 at 0.15% (aerosol hair spray), Ceteth-29 at <1% (hair conditioners), Ceteth-20 between 0.1–1%, and various Ceteths of undisclosed length up to 2.5% (CTFA 1995). Note that Ceteth-29, although reported to be used, is not listed in the 1997 *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger and McEwen 1997).

International

Ceteths are listed in the *Comprehensive Licensing Standards of Cosmetics by Category (CLS)* and must conform to the specifications stipulated in the *Japanese Standards of Cosmetic Ingredients* (Yakuji Nippo, Ltd. 1994). They can be used in all CLS categories without restrictions.

Noncosmetic

Ceteths are used for their emulsifying, wetting, antistatic, solubilizing, defoaming, detergent, and lubricating properties in pharmaceutical and industrial applications (Budavari 1989).

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

In general, long-chain aliphatic alcohols (such as cetyl alcohol) are oxidized to their corresponding fatty acids in mammalian tissues. In studies with rats administered radioactive cetyl alcohol by either stomach tube or thoracic duct fistulas, most of the radioactivity was found in the thoracic duct lymph, indicating good absorption. Some of the cetyl alcohol was eliminated unchanged in waste products, but most of the cetyl alcohol was oxidized to palmitic acid and incorporated into triglycerides and phospholipids (Elder 1988).

Blood Effects

Azaz, Segal, and Milo-Goldzweig (1981) demonstrated that complete hemolysis occurred when Ceteth-20 (8 μM–1.1 mM) was added to a suspension of fresh rat erythrocytes, regardless of concentration. The possibility that peroxides were involved was investigated by Segal and Milo-Goldzweig (1983) using specific inhibitors and inactivators. The hydroxyl radical was the only apparent oxygen species of peroxides to participate in hemolysis.

Barton (1978) investigated the effects of Ceteth-20 on platelet aggregation, release, and clotting activity. Ceteth-20 inhibited platelet aggregation and the release of serotonin, Ca^{2+}, and labile aorta-contracting substance. It interfered with clotting activity by shortening of Stypven time and the activated Factor X clotting time.

ANIMAL TOXICOLOGY

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 smaller 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 also were 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, or 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-6-32 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-6-32, at doses up to 1.69 g/kg/day in the chronic study (Andersen 1993).

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 1988).

Acute Oral Toxicity

The oral LD_{50} (rat) was >25.1 g/kg for Ceteth-2, 3.5 g/kg (males) and 2.5 g/kg (females) for Ceteth-10, and 3.59 g/kg for Ceteth-20 (STN International 1988; 1991).

Short-Term Dermal Toxicity

A 2 g/kg dose of a cleansing formulation containing 2.5% Ceteth-2 was applied to the back of a group of 10 New Zealand albino rabbits (five of each sex). The hair had been clipped prior to application. The area of exposure was abraded at weekly intervals; the abrasions were such that the stratum corneum was penetrated without disturbing the dermis or inducing bleeding. The test material was applied 5 days a week for a total of 20 applications (four-week study). Daily observations were made

and a blood sample was obtained 24 days after the first application. Animals were killed at the end of the study and various organs examined. No significant differences were found in body weight, physical appearance, behavior, and survival in the dosed animals as compared to untreated controls. The dosed animals did experience weight loss during the first 10 days of the study and had less of a weight gain by the end of the study. This weight loss was considered to result from developing skin irritation to which the animals adjusted after the initial ten days. Moderate erythema was noted in all animals of the Ceteth-2 dosing group during the first week of application. Thereafter, moderate erythema with swelling, wrinkling, cracking, and drying skin was noted for the duration of the study. Although most serum parameters remained comparable to control values, animals of the Ceteth-2 group did have significantly ($p < .05$) decreased serum alkaline phosphatase activity (SAP). However, no lesions were noted with regard to the liver and kidneys and the changes in SAP were considered unrelated to dosing. No changes were noted with regard to absolute and relative organ weight and no systemic effects were noted (CTFA 1975a).

Two suntan lotions each containing 3.0% Ceteth-2 were applied to groups of 10 female albino rats. The protocol followed was similar to that described above except that the shaved skin of the rats was not abraded, the dose administered at each application was 500 mg/kg, and a blood sample was obtained at the termination of the study. In addition to examination of various organs, bone marrow slides were also prepared at the end of the study. No changes in external appearance were noted at the site of application. Rats which received one suntan formulation had significantly ($p < .05$) higher mean hemoglobin values as compared to untreated controls. However, the value remained within the range for historical controls and was not considered treatment related. Although rats of this treatment group had a significantly ($p < .05$) higher value for the liver to body weight ratio (2.8 versus 2.7 for the control group), the researchers reported no systemic effects (CTFA 1975b).

Dermal Irritation

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).

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 1988).

In a study by Mezei et al. (1966), Ceteth-2 and Ceteth-10 (0.3 g) were applied daily to the shaved abdomens of New Zealand white rabbits at concentrations of 1, 5, 10, 60, and 100% (the vehicles used included water, hydrophilic ointment, and petrolatum). The rabbits were examined daily, but data were supplied only for days 3 and 10. Biopsies were taken from the treated skin on days 10 and 30, and at the termination of the study (several animals were used in long-term studies and had the test material applied for an additional 1 to 4 months). A new site was used for each biopsy.

After 3 days of exposure, erythema and edema were noted in animals treated with 1 or 5% Ceteth-2 in either a petrolatum or hydrophilic petrolatum vehicle. Similar changes were noted in animals treated with 1 or 5% Ceteth-10 in a petrolatum, water or hydrophilic ointment vehicle. Thickening was noted in animals treated with 10% concentrations of either Ceteth-2 or Ceteth-10 in petrolatum; erythema and edema were noted with the 10% Ceteths in water. With regard to the 60% solution, Ceteth-2 caused thickening when administered in either hydrophilic petrolatum or water; Ceteth-10 caused similar changes when applied in either a hydrophilic ointment or water vehicle. Both Ceteths caused thickening when applied at 100%.

After 10 days of exposure, changes continued to be noted for both Ceteth solutions at all tested concentrations. Pronounced irritation was observed in animals treated with Ceteth-2; the 5% solution in petrolatum caused intense erythema and edema and the 10% solution in petrolatum caused intense hyperkeratinization. Solutions of 10% Ceteth-10 in either petrolatum or hydrophilic ointment and solutions of 60% Ceteth-2 in hydrophilic petrolatum produced fissures and open lesions. Both solutions applied at 100% strength produced severe fissures and lesions after 10 days of exposure. Microscopic changes were in accordance with gross observations; oxygen consumption by the treated skin increased three- to fourfold. The hydrophilic ointment vehicle produced no irritation when tested alone; both petrolatum and hydrophilic petrolatum produced erythema and edema when applied to animals as vehicle controls (Mezei et al. 1966).

In a single insult occlusive patch assay, 2.5% Ceteth-2 tested in a cleansing formulation produced erythema and edema scores of 1 in five rabbits and a score of 2 in one rabbit at the 24-hour postunwrapping observation. The maximum possible score is 8. By the 72-hour observation, one rabbit had a total score of 1, reactions in four rabbits were scored as 2, and the reaction in the sixth rabbit was scored as 3. The sixth rabbit had received a score of 1 at the 24-hour observation. The rabbit which was scored as a 2 at 24 hours received the same score at the 72-hour observation. The formulation was considered to have minimal irritation potential (CTFA 1974a).

Ocular Irritation

In an ocular irritation assay, 2.5% Ceteth-2 tested in formulation produced average irritation scores of 1 (maximum 110) in six rabbits 1 day after instillation. No reaction was noted on day 2 (CTFA 1974b).

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).

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 1988).

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, aka 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 (Cosmetic Ingredient Review 1996). In summary, this report concluded that the ethylene glycol monoalkyl ethers are not themselves toxic, but rather that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, the report also concluded that the toxicity of the monoalkyl ethers is inversely proportional to the length of the alkyl chain (methyl is more toxic than ethyl than propyl than butyl, etc.).

Given the methods of manufacture of the Ceteth compounds, the Panel concluded there is no likelihood of methoxyethanol, ethoxyethanol, etc., being present as an impurity. Because there likely would be ethylene glycol monomer linked by an ether group to the Ceteth moiety in preparation of the shorter chain Ceteths, and because Ceteth-1 itself is listed as a cosmetic ingredient, it is appropriate to evaluate the potential toxicity of Ceteth-1. Even if linked to ethylene glycol monomer, however, the Panel concluded that it is unlikely that the Ceteth 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 Ceteth moieties suggested to the Expert Panel that there is no reproductive or developmental hazard posed by these Ceteth compounds. In addition, many of the Ceteths will contain only a polyethylene glycol base, further reducing the potential for adverse effects of the kind seen for ethylene glycol monoalkyl ethers.

MUTAGENICITY

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).

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

Ceteth-20 was tested in a spot test that detected enhanced transposition of Tn*9* in *Escherichia coli*. Phage λ:: Tn*9*-infected cells were plated on chloramphenicol media and one to two drops of Ceteth-20 (0.1%) were placed on the plate. Chloramphenicol-resistant colonies were attributed to the transposition of Tn*9* to the bacterial chromosome. Ceteth-20 enhanced transposition threefold. However, when palmitic acid was added with Ceteth-20, the stimulating effect was not observed, suggesting that lipid or membrane was involved in the transposition process (Datta, Randolph, and Rosner 1983).

CARCINOGENICITY

All of the carcinogenicity data available on the PEGs were specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosing, 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

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

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 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 1988).

DISCUSSION FROM PREVIOUS REPORTS

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 causative agent in both animal and human studies. However, there was neither evidence of systemic toxicity nor 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).

In its review of cetyl alcohol, the Expert Panel concluded that this ingredient was safe for use as a cosmetic ingredient. 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 1988).

SUMMARY

Ceteths 1–45 are the polyethylene glycol (PEG) ethers of cetyl alcohol (Ceteth-1 is the ethylene glycol ether). They are used in cosmetic formulations as surfactants; in January 1996 there were 259 reported uses for the various Ceteths. Recent data suggest that Ceteths are used at a maximum concentration of 5%.

PEGs appear to be readily absorbed through damaged skin. Gastrointestinal absorption is dependent on the molecular weight of the PEG compound. Orally administered Cetyl Alcohol was absorbed and oxidized to palmitic acid.

Ceteth-20 induced complete hemolysis of rat erythrocytes. Ceteth-20 also inhibited platelet aggregation and the release of serotonin, Ca^{2+}, and interfered with clotting activity.

PEGs have low oral and dermal toxicity with greater MW PEGs appearing to be less toxic than lighter PEGs. The oral LD_{50} for Cetyl Alcohol was >8.2 g/kg. Dermal irritation ranging from mild inflammation to dermal infiltrates of histiocytes was noted for Cetyl Alcohol concentrations of 2.0 and 30.0%, respectively. In inhalation studies, slight irritation was observed in mice, rats, and guinea pigs after a single 6-hour exposure to Cetyl Alcohol vapor (26 ppm), but no treatment-related changes were noted after repeated 10 minute exposure to 9.6 mg/L.

Oral LD_{50} values for Ceteths range from 3.5 g/kg for Ceteth-10 and Ceteth-20 to >25.1 g/kg for Ceteth-2.

A cleansing formulation containing 2.5% Ceteth-2 was irritating to abraded rabbit skin following repeated exposure but did not produce systemic effects. This same material produced mild erythema and edema in rabbits when applied in a single occlusive patch. A suntan lotion containing 3.0% Ceteth-2 caused neither irritation nor systemic effects when applied on the intact skin of rats.

PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. In some dermal studies on formulations containing Cetyl Alcohol, well-defined erythema was noted.

Dose-dependent and vehicle-dependent dermal irritation was noted in rabbits exposed to 5, 10, 60, or 100% Ceteth-2 and Ceteth-10.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the Ceteth compounds would cause reproductive or teratogenic effects based on their chemical and structural characteristics.

Various mutagenicity assays on PEGs and Cetyl Alcohol were negative. Ceteth-20 was found to enhance transposition of Tn*9* in *E. coli*; this effect was not observed when palmitic acid was also added.

Carcinogenicity studies in which various PEGs were used as solvent controls were negative.

DISCUSSION

In assessing the safety of the Ceteth group, the CIR Expert Panel relied extensively on earlier safety evaluations of the parent compounds, cetyl alcohol and polyethylene glycol. In addition, the submission of recent concentration of use data by the cosmetics industry precluded the need for additional testing. The Expert Panel decided that the Ceteth group is safe for use in cosmetic formulations.

The Panel noted that the stipulation stated in the PEG safety evaluation, "not to be used on damaged skin," also applies to this ingredient group. It was noted that in studies on Ceteth-2, a 2.5% concentration in a cleansing formulation was irritating when applied to abraded rabbit skin or under conditions of occlusive dermal exposure. However, 3.0% Ceteth-2 in a suntan formulation did not cause dermal changes when applied to intact rat skin.

As described earlier in this report, the possibility of reproductive and developmental effects was assessed and determined not to be a concern.

Further, in the absence of impurities data, the Panel cautioned that a Ceteth preparation should not contain 1,4-dioxane or ethylene oxide which are possible oxidation products.

The Panel acknowledged the use of Ceteths in hair sprays. They also noted that inhalation studies on Cetyl Alcohol demonstrated mucosal irritation in rats and guinea pigs following a single 6-hour exposure to 26 ppm. However, no treatment-related changes were observed following repeated 10-minute exposures to Cetyl Alcohol at 9.6 mg/L. Further, based on particle size and cosmetic use concentrations, it was not considered that these ingredients, in formulation, are respirable. Thus, the Panel

considered the Ceteth group to be safe for use in aerosolized products.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that Ceteth-1, -2, -3, -4, -5, -6, -10, -12, -14, -15, -16, -20, -24, -25, -30, and -45 are safe in the present practices of use.

REFERENCES

Andersen, F. A., ed. 1993. Final report on the safety assessment of polyethylene glycols (PEGs)-6, -8, -32, -75, -150, -14M, -20M. *J. Am. Coll. Toxicol.* 12:429–457.

Argus, M. F., J. C. Arcos, and C. Hoch-Ligeti. 1965. Studies on the carcinogenic activity of protein-denaturing agents: Hepatocarcinogenicity of dioxane. *J. Natl. Cancer. Inst.* 35:949–958.

Azaz, E., R. Segal, I. Milo-Goldzweig. 1981. Hemolysis caused by polyoxyethylene-derived surfactants. *Biochim. Biophys. Acta* 646:444–449.

Barton, P. G. 1978. Effects of a polyoxyethylene detergent (Brij 58) on platelet aggregation, release and clotting activity. *Biochim. Biophys. Acta* 539:98–113.

Budavari, S., ed. 1989. *The Merck index. An encyclopedia of chemicals, drugs, and biologicals*, 11th ed., 1206. Rahway, NJ: Merck & Co.

Cosmetic Ingredient Review (CIR). 1996. *Special report on the reproductive and developmental toxicity of ethylene glycol and its ethers.* Washington, DC: CIR.[2]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1974a. Primary Skin Irritation: Ceteth-2. Test #: 07-074. Unpublished data submitted by CTFA in August, 1995. 1 page.[2]

CTFA. 1974b. Eye Irritation: Ceteth-2. Test #: 22-107. Unpublished data submitted by CTFA in August, 1995. 1 page.[2]

CTFA. 1975a. Four week subacute dermal toxicity study in rabbits: Ceteth-2. Unpublished data submitted by CTFA in August, 1995. 7 pages.[2]

CTFA. 1975b. Four week subacute dermal toxicity study in rats: Ceteth-2. Unpublished data submitted by CTFA in August, 1995. 9 pages.[2]

CTFA. 1995. Use levels for various ingredients. Unpublished data submitted by CTFA in July, 1995. 2 pages concerning Ceteths.[2]

Datta, A. R., B. W. Randolph, and J. L. Rosner. 1983. Detection of chemicals that stimulate Tn9 transposition in *Escherichia coli* K12. *Mol. Gen. Genet.* 189:245–250.

Elder, R. L., ed. 1983. Final report on the safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates. *J. Am. Coll. Toxicol.* 2:17–34.

Elder, R. L., ed. 1988. Final report on the safety assessment of Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol. *J. Am. Coll. Toxicol.* 7:359–413.

Food and Drug Administration (FDA). 1984. Cosmetic product formulation and frequency of use data. *FDA database.* Washington, DC: FDA.

FDA. 1992. Modification in voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements. *Federal Register* 57:3128–3130.

FDA. 1996. Frequency of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

Hamburger, R., E. Azaz, and M. Donbrow. 1975. Autoxidation of polyoxyethyleneic non-ionic surfactants and of polyethylene glycols. *Pharm. Acta Helv.* 50:10–17.

Hoch-Ligeti, C., M. F. Argus, and J. C. Arcos. 1970. Induction of carcinomas in the nasal cavity of rats by dioxane. *Br. J. Cancer* 24:164–167.

Kociba, R. J., S. B. McCollister, C. Park, T. R. Torkelson, and P. J. Gehring. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. *Toxicol. Appl. Pharmacol.* 30:275–286.

McGinity, J. W., J. A. Hill, and A. L. La Via. 1975. Influence of peroxide impurities in polyethylene glycols on drug stability. *J. Pharm. Sci.* 64:356–357.

Mezei, M., R. W. Sager, W. D. Stewart, and S. L. Deruyter. 1966. Dermatitic effect of nonionic surfactants I. Gross, microscopic, and metabolic changes in rabbit skin treated with nonionic surface-active agents. *J. Pharm. Sci.* 55:584–590.

Rempe, J. M., and L. G. Santucci, eds. 1992. *CTFA list of Japanese cosmetic ingredients*, 2nd ed. Washington, DC: The Cosmetic, Toiletry and Fragrance Association.

Robinson, J. J., and E. W. Ciurczak. 1980. Direct gas chromatographic determination of 1,4-dioxane in ethoxylated surfactants. *J. Soc. Cosmet. Chem.* 31:329–337.

Scientific and Technical Information Network (STN) International. 1988. Properties of Ceteth-10—Material safety data sheet. *Canadian Occupational Health and Safety database file.* Columbus, OH: STN-International.

STN International. 1991. Properties of Ceteth-2—Material safety data sheet. *Candian Occupational Health and Safety database file.* Columbus, OH: STN-International.

Segal, R., and I. Milo-Goldzweig. 1983. Hemolysis caused by Cetomacrogol 1000: Evidence for hydroxyl radical participation. *J. Pharm. Sci.* 72:1461–1464.

Silverstein, B. D., P. S. Furcinitti, W. A. Cameron, J. E. Brower, and O. White, Jr. 1984. *Biological effects summary report—Polyethylene glycol.* National Technical Information Service No. DE84007984.

Wenninger, J. A., G. N. McEwen, Jr. eds. 1997. *International cosmetic ingredient dictionary and handbook*, 7th ed., vol. 1, 229–232. Washington, DC: The Cosmetic, Toiletry, and Fragrance Association.

Yakuji Nippo, Ltd. 1994. *The comprehensive licensing standards of cosmetics by category 1994 (CLS 1994)*, 74–75. Tokyo, Japan: Yakuji Nippo, Ltd.

[2]Available for review: Director, Cosmetic Ingredient Review, 1101 17th St., NW, Suite 310, Washington, DC 20036-4702.