Final Report on the Safety Assessment of Oleth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50[1]

The Oleth family of ingredients are the polyethylene glycol (PEG) ethers of oleyl alcohol. They are manufactured by the ethoxylation of oleyl 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. Oleths are surfactants used as emulsifying, cleansing, and solubilizing agents in cosmetic formulations. Limited safety test data are available on ingredients in the Oleth family, all consistent with surfactant properties. In feeding studies, Oleth-20 was associated with reduced body weight gain. Hepatic lesions in one exposure group were not found in any other exposure group, but were found in the controls. Oleth-20 and Oleth-10 were found to have moderate ocular irritation potential, and Oleth-10 was considered to be a cumulative skin irritant. Toxicity data, including reproductive and developmental toxicity, carcinogenesis data, and clinical testing data, available from previous safety assessments on Polyethylene Glycol and Oleyl Alcohol, were summarized. The principal finding related to PEGs, based on clinical data in burn patients, is that PEGs were mild irritant/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. Although metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, it was considered unlikely that the relevant metabolites would be found in or produced from the use of Oleths 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. Based on particle size and cosmetic use considerations, it was not considered that these ingredients, in formulation, are respirable. Based in part on the limited data available on Oleths included in the report and on the previous reviews of Polyethylene Glycol and Oleyl Alcohol, it was concluded that Oleth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50 are safe in the present practices of use.

The following report is a review of the safety data on Oleths-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50, which are surfactants used in cosmetics as emulsifying, cleansing, and solubilizing agents. Chemically, these ingredients are the polyethylene glycol (PEG) ethers of oleyl 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).
>
> *Oleyl Alcohol* is safe as currently used in cosmetics (Elder 1985). At the time of the CIR review, Oleyl Alcohol was reported to be used at concentrations >0.1 to >50%.

Because there are limited data specifically on the Oleth family, the relevant data from the Final Reports on the PEG family and oleyl alcohol have been extracted and summarized in this review as a basis for the assessment of safety of Oleths 2–50. *Summaries of studies contained in these earlier reviews appear in italicized font.*

CHEMISTRY

Definition and Structure

Oleth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50 (CAS No. 9004-98-2 [generic]) are the polyethylene glycol (PEG) ethers of oleyl 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). Oleyl Alcohol is a mixture of fatty alcohols that consists primarily of the straight-chain unsaturated 9-*n*-octadecenol (Elder 1985).

Oleths are identified in Japan as polyoxyethylene oleyl ether (Rempe and Santucci 1992).

Chemical and Physical Properties

The Oleth 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 many hydrocarbons. Solubility in water increases with the content of ethylene oxide (Budavari 1989).

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[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.

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$$CH_3(CH_2)_7CH = CH(CH_2)_7CH_2(OCH_2CH_2)_nOH$$

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

Method of Manufacture

Oleths are manufactured by the ethoxylation of oleyl 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).

USE

Cosmetic

The Oleths are surfactants used as emulsifying, cleansing, and solubilizing agents (Wenninger and McEwen 1997). Table 1 shows the product formulation data submitted to the Food and Drug Administration (FDA) in January 1996. These ingredients were collectively used in over 600 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 highest concentration used was 25%. At this concentration, Oleth-2 and Oleth-10 were used in tonics, dressings, and other hair grooming aids, Oleth-10 were used in blushers, and Oleth-20 was used in colognes/toilet waters (FDA 1984). Recent data submitted directly by CTFA indicated that Oleths are used at concentrations up to 12%. The data indicated the following maximum concentrations of use for specific Oleths in particular formulations: Oleth-2 up to 12% (hair styling gel), Oleth-10 between 0.2–6.0% (various formulations, used at 6% in sachets), Oleth-16 up to 5%, and Oleth-20 up to 12% (various formulations) (CTFA 1995).

International

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

Noncosmetic

Oleths 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 to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

The metabolism of oleyl alcohol has been well documented. Following both intravenous and oral administration, oleyl alcohol is rapidly used for biosynthesis of lipids and other naturally occurring cellular constituents or enters into metabolic pathways for energy production (Elder 1985).

The Oleths increased the permeability of isolated human stratum corneum in in vitro studies. Although the underlying mechanism of this effect was not determined, the data suggested that the enhancement effect by oxyethylene oleyl ethers maximizes at an optimal oxyethylene chain length or head group size between 2 and 10 oxyethylene units (Kadir et al. 1993).

Cytotoxicity

Cytotoxicity assays using human keratinocyte and fibroblast cultures were conducted to determine the potential dermal toxicity of Oleth-10 and other compounds used as skin penetration enhancers. In a proliferation inhibition assay, 72,500 fibroblasts/well and/or 50,000 keratinocytes together with 100,000 lethally irradiated (3000R) 3T3 cells/well were inoculated in

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

Product category	Total no. formulations in category	Total no. of formulations containing ingredient
Oleth-2		
Bath oils, tablets, and salts	147	2
Bubble baths	211	1
Hair conditioners	715	3
Permanent waves	434	2
Rinses (noncoloring)	66	1
Tonics, dressings, and other hair grooming aids	604	2
Moisturizing preparations	942	2
Skin fresheners	244	1
1996 total for Oleth-2		**14**
Oleth-3		
Hair conditioner	715	3
Permanent waves	434	2
Foot powders and sprays	33	1
Moisturizing preparations	942	2
Night preparations	226	1
Other skin care preparations	810	2
1996 total for Oleth-3		**11**
Oleth-5		
Other bath preparations	166	1
Other fragrance preparations	195	3
Hair conditioners	715	6
Shampoos (noncoloring)	972	1
Wave sets	95	1
Other hair preparations	395	1
Aftershave lotion	268	1
Moisturizing preparations	942	5
Night preparations	226	2
Other skin care preparations	810	4
Suntan gels, creams, and liquids	196	1
1996 total for Oleth-5		**26**
Oleth-8		
Permanent waves	434	7
Shampoos (noncoloring)	972	1
1996 total for Oleth-8		**8**
Oleth-9		
Bath oils, tablets, and salts	147	2
1996 total for Oleth-9		**2**
Oleth-10		
Bath oils, tablets, and salts	147	1
Eyeliner	533	2
Other eye makeup preparations	136	1
Colognes and toilet waters	834	7
Hair conditioners	715	1
Hair straighteners	50	1
Permanent waves	434	2
Shampoos (noncoloring)	972	1
Tonics, dressings, and other hair grooming aids	604	2
Wave sets	95	1
Other hair preparations	395	4
Hair dyes and colors (requiring caution statement and patch test instructions)	1612	21
Foundations	355	1
Makeup bases	154	1
Bath soaps and detergents	372	1
Aftershave lotion	268	2
Other shaving preparation products	63	2
Cleansing preparations	820	8
Depilatories	53	1
Face and neck prepartions (excluding shaving preparations)	300	4
Body and hand preparations (excluding shaving preparations)	1012	6
Moisturizing preparations	942	7
Night preparations	226	2
Paste masks (mud packs)	300	5
Skin fresheners	244	5
Other skin care preparations	810	7
Other suntan preparations	68	1
1996 total for Oleth-10		**97**
Oleth-15		
Eyeliner	533	2
Deodorants	303	1
1996 total for Oleth-15		**3**
Oleth-16		
Other bath preparations	166	1
Hair conditioners	715	1
Shampoos (noncoloring)	972	2
Tonics, dressings, and other hair grooming aids	604	5
Moisturizing preparations	942	4
1996 total for Oleth-16		**13**

(Continued on next page)

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

Product category	Total no. formulations in category	Total no. of formulations containing ingredient	Product category	Total no. formulations in category	Total no. of formulations containing ingredient
Oleth-20			**Oleth-20 (cont.)**		
Other baby products	37	4	Other shaving preparation products	63	6
Bubble baths	211	3	Cleansing products	820	11
Eyeliner	533	2	Body and hand preparations (excluding shaving preparations)	1012	6
Colognes and toilet waters	834	3	Moisturizing preparations	942	6
Perfumes	286	1	Paste masks (mud packs)	300	4
Hair conditioners	715	24	Skin fresheners	244	12
Hair sprays (aerosol fixatives)	334	1	Other skin care preparations	810	13
Hair straighteners	50	5	**1996 total for Oleth-20**		**224**
Permanent waves	434	40	**Oleth-25**		
Shampoos (noncoloring)	972	2	Body and hand preparations (excluding shaving preparations)	1012	1
Tonics, dressings, and other hair grooming aids	604	29	Moisturizing preparations	942	2
Wave sets	95	10	**1996 total for Oleth-25**		**3**
Other hair preparations	395	114	**Oleth-30**		
Hair dyes and colors (requiring caution statement and patch test instructions)	1312	4	Hair dyes and colors (requiring caution statement and patch test instructions)	1612	180
Makeup bases	154	3	Hair color sprays (aerosol)	19	17
Nail creams and lotions	18	1	Hair bleaches	113	2
Deodorants	18	1	Body and hand preparations (excluding shaving preparations)	1012	1
Other personal cleanliness products	339	4	**1996 total for Oleth-30**		**200**
Aftershave lotion	268	7			
Beard softeners	4	1			
Men's talcum	11	1			
Shaving cream	158	3			

a six-well cluster. The medium was removed 1 day later (fibroblasts) and/or 2 days later (keratinocytes), and the cells were fed culture medium with various concentrations of Oleth-10. The cultures were trypsinized on day 4 and the number of cells was counted the following day using a Rosenthal-Fuchs chamber. Oleth-10 inhibited 50% of the fibroblast and keratinocyte proliferation at concentrations of 0.017 mM and 0.0025 mM, respectively (Ponec et al. 1990).

In order to investigate changes in the morphology of fibroblasts and keratinocytes caused by Oleth-10, confluent cell cultures were treated with a range of concentrations of Oleth-10, and morphological changes were monitored using light microscopy. If changes occurred 24 hours after administration, the test culture medium was removed and replaced with medium alone to allow for reversibility of toxic effects. Oleth-10 caused irreversible morphological changes in fibroblasts and keratinocytes at concentrations of 0.05 mM and 0.008 mM, respectively. These alterations included gradual detachment of cells from culture and changes in cell shape (Ponec et al. 1990).

An assay was also conducted to test Oleth-10's ability to inhibit fibroblast-induced collagen contraction. Under optimized conditions, Oleth-10 was added to a collagen lattice (75,000 cells) and contraction was evaluated 72 hours later. Oleth-10 was routinely added 1 hour after casting the collagen solution to prevent interference with the collagen gel formation process. At a concentration of 0.026 mM, Oleth-10 caused 50% contraction inhibition (Ponec et al. 1990).

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, 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-6-32 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).

A formulation containing 20% Oleyl alcohol had an LD_{50} value of >10 g/kg in rats. Studies with similar long-chain alcohols indicated that oleyl alcohol is also likely to have low dermal toxicity (Elder 1985).

Acute Oral Toxicity

Oleth-10 had an oral LD50 of >5.0 g/kg in rats (CTFA 1976a).

Subchronic Oral Toxicity

A 90-day feeding study of Oleth-20 was conducted using Sherman Wistar rats. Groups of 15 rats were fed diets containing 0.01, 0.04, 0.16, 0.64, 2.5, and 5.0% Oleth-20. The high dose group was originally fed 10.0% Oleth-20, but the rats stopped eating after 1 week, so the concentration was reduced. A control group of 30 rats was fed untreated feed. Body weight gain and feed consumption were measured weekly. Two rats of each sex were used for hematology studies at monthly intervals during the study, as well as before the start of the experiment. At week 8, the two smallest animals of each sex in each dose group were killed for necropsy. The remaining animals were kept on the diet and were killed for necropsy at the end of the study. Body weight gain was significantly reduced in the male rats fed the 2.5% and 5.0% Oleth-20 diets and in the female rats fed the 5.0% Oleth-20 diet. These observations corresponded to the decreased feed intake of these animals. No significant changes in hematology parameters were observed, and no significant increases were observed in the number or types of gross or microscopic lesions (Industrial Biology Research and Testing Laboratories 1993a).

In another study, three Beagle dogs were fed diets containing 0.04, 0.64, or 5.0% Oleth-20 for 90 days. Three control dogs were fed stock diet. Feed consumption and body weight gain were monitored weekly, and blood studies were conducted regularly, during as well as before the start of the experiment. All of the animals were killed at the end of the study for necropsy. The dog fed the 5.0% Oleth-20 diet gained during the study about half as much weight as the control dogs. Body weight gain in the dogs fed the lower dose diets was comparable to that of the controls. Feed intake paralleled these observations. Hematology parameters were normal in the treated dogs, and no consistent lesions were observed at gross and microscopic examination. The investigators noted that the dog fed the 0.64% Oleth-20 diet had hepatic lesions suggestive of a toxic etiology. However, it was noted that these lesions were not observed in the other treated dogs, and that some hepatic lesions were found in the control group and consisted of perilobular cellular infiltration and parasitic granulomas (Industrial Biology Research and Testing Laboratories 1993b).

Dermal Irritation

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).

In tests with rabbits, oleyl alcohol produced minimal to mild primary cutaneous irritation. In one assay system, the skin irritancy of technical grade oleyl alcohol was moderate to severe in rabbits, guinea pigs, and rats, but no irritation was observed in swine and human skin. Observations made in a subchronic skin irritation study indicated that 100% oleyl alcohol was "poorly tolerated" when applied to the skin of rabbits daily for 60 days, whereas a 10% dilution was "relatively well tolerated." Results of sensitization studies of other long-chain alcohols indicated little sensitization potential (Elder 1985).

A single application of 10% aq. Oleth-20 (0.5 ml; pH = 6.0–8.0) was made using 24-hour occlusive patches to both abraded and intact shaved skin sites of six New Zealand white rabbits. The sites were observed for erythema, edema, and other effects 24 and 72 hours after application, and the mean scores were averaged. The primary irritation index was 6.50/8. Oleth-20 was considered a primary dermal irritant (Consumer Product Testing Company, Inc. 1982).

In a single-insult, open patch test, Oleth-20 tested at 50% produced Primary Irritation Index (PII) scores of 1 in four rabbits and 2 in two rabbits at the 24-hour observation. The maximum possible score is 8. At 48 hours, scores of 1 were recorded for four rabbits (three of which also were scored 1 at 24 hours, the fourth had a score of 2 at 24 hours) and two rabbits had a score

of 2 (one of which had a score of 1 at 24 hours). At 72 hours, four rabbits had a score of 1 (two had been scored 1 throughout the study) and two rabbits had a score of 2. Oleth-20, when tested at 50% using an open patch, had minimal irritation potential (CTFA 1972c).

In a single-insult occlusive patch test, undiluted Oleth-10 produced a total PII score of between 0.5 and 1 in five rabbits at the 2-hour postremoval observation. At the 24-hour observation, the reactions were more severe, producing scores between 1 and 3. Oleth-10 had minmal irritation potential (CTFA 1976c).

In a similar assay, undiluted Oleth-10 produced total PII scores of 2 in nine rabbits at the 2 h postremoval observation, and scores from 0.5 to 2 at the 24-hour observation. Oleth-10 had mild irritation potential (CTFA 1976d).

Ocular Irritation

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).

Oleth-20 was not an irritant when tested using the Draize rabbit eye irritation test. Eleven separate tests were conducted on groups of six rabbits. One conjunctival sac of each animal was instilled with 0.1 ml 5% Oleth-20, and the eyes were examined 24, 48, and 72 hours, and 7 days later. After 24 hours, the eyes were examined after fluorescein staining. Very mild conjunctival redness and chemosis were present at the 24-hour scoring period. These changes had disappeared after 48 hours (Marzulli & Ruggles 1973).

In another study, 0.1 ml Oleth-20 (70% active) was instilled into one conjunctival sac of nine New Zealand white rabbits. The contralateral eye was left untreated to serve as the control. The eyes of three rabbits were rinsed 30 seconds after instillation, while the eyes of the remaining rabbits were left unrinsed. Observations for irritation were made 24, 48, and 72 hours, and 4 and 7 days postinstillation. Oleth-20 was a moderate ocular irritant. The irritation scores of a maximum possible score of 110 were, 32.7 at 24 hours, 27.8 at 48 hours, 20.8 at 72 hours, 18.5 at day 4, and 13.8 at day 7. The severity of irritation was reduced in the rinsed eyes; the scores were 10.0, 4.7, 3.3, 1.3, and 0.7, respectively (Consumer Product Testing Company, Inc. 1982).

Oleth-20, tested at 50%, produced average irritation scores of 7, 5, 5, 5, and 2 on days 1, 2, 3, 4, and 7 after instillation, respectively. The maximum possible score is 110; Oleth-20 had moderate irritating potential (CTFA 1972a).

Oleth-10, tested undiluted and not rinsed from the eye after instillation, produced an average ocular irritation score of 10 (maximum 110) and a total score of 18 in six rabbits one day after instillation. Average scores of 18, 8, 10 and 4 and total scores of 29, 13, 23, and 8 were recorded on days 2, 3, 4 and 7 respectively. Oleth-10 was considered a moderate irritant (CTFA 1972b).

In a second assay using six rabbits, undiluted Oleth-10 produced average irritation scores of 14, 14, 11, and 6 and total irritation scores of 36, 32, 22, and 12 on days 1, 2, 4 and 7 after instillation, respectively (CTFA 1976b).

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 (CIR 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 Oleth 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 Oleth moiety in preparation of the shorter chain Oleths, and because Oleth-1 (although not itself a cosmetic ingredient) may be present in these shorter chain preparations, it is appropriate to evaluate the potential toxicity of Oleth-1. Even if linked to ethylene glycol monomer, however, the Panel concluded that it was unlikely that the Oleth 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 Oleth moieties suggested to the Expert Panel that there is no reproductive or developmental hazard posed by these Oleth compounds. In addition, many of the Oleths 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).

An Ames test of a long-chain alcohol similar to oleyl alcohol had negative results (Elder 1985).

CARCINOGENICITY

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).

A long-chain alcohol similar to oleyl alcohol was not a tumor promoter in mice treated with DMBA (Elder 1985).

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).

For oleyl alcohol, the results of screening patch tests for contact sensitization in large populations indicated a rate of 0.60%. Tests of product formulations in humans demonstrated low potentials for significant skin irritation or sensitization from these types of alcohols in formulation. Photoreactivity studies on products containing 2.5% oleyl alcohol were negative for phototoxicity or photosensitization. A hair-dressing product containing 1.5% oleyl alcohol was nonirritating to the human eye (Elder 1985).

In a 21-day cumulative irritancy assay, a cologne stick containing 3% Oleth-10 was applied to the same site on the back of eight panelists. Five of the panelists had no reactions noted after any of the 21 applications, two others had total scores of 3.5 and 8.5 respectively, and the eighth panelist had a total score of 27.5 out of a maximum possible score of 84 (maximum daily score of 4 times 21 days) (CTFA 1976e).

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 for 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.

In its review of oleyl alcohol, the Expert Panel concluded that this ingredient was safe for use in cosmetic formulations.

SUMMARY

Oleths 2-45 are the polyethylene glycol (PEG) ethers of oleyl alcohol. Oleths are used in cosmetic formulations as surfactants; in January 1996 they were used in over 600 formulations.

PEGs appear to be readily absorbed through damaged skin. Gastrointestinal absorption is dependent on the molecular weight of the PEG compound. Following intravenous and oral administration, oleyl alcohol is rapidly used for biosynthesis of lipids and other cellular constituents. The Oleths increased permeability of isolated human stratum corneum in in vitro studies.

In a proliferation inhibition assay, Oleth-10 inhibited fibroblast and keratinocyte proliferation.

PEGs have low oral and dermal toxicity with larger molecular weight PEGs appearing to be less toxic than smaller PEGs. The oral LD50 for 20% Oleyl Alcohol was >10 g/kg in rats.

In a 90-day feeding study, body weight gains were significantly less in male and female rats of the 5% Oleth-20-dose group as well as in males of the 2.5% Oleth-20 group. Hematologic parameters were normal in treated rats and no significant increase in lesions was observed at gross and microscopic examination. Similar findings were reported in studies with dogs.

PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. In studies using various concentrations of Oleth-10 and Oleth-20, both had dermal irritation potential, especially when tested on abraded skin or under occlusive patch conditions.

Oleth-20 at 5% concentration produced very mild transient conjunctival redness and chemosis; at 70% active, it was considered a moderate ocular irritant. Other studies considered Oleth-10 to have moderate ocular irritation potential.

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

Various mutagenicity assays of PEGs and Oleyl Alcohol were negative. Carcinogenicity studies in which various PEGs were used as solvent controls were negative.

In a clinical study of a commercial product, Oleth-10 produced cumulative irritation in three of eight panelists.

DISCUSSION

In assessing the safety of the Oleth group, the CIR Expert Panel relied extensively on earlier safety evaluations of the parent compounds, oleyl 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 Oleth 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. Dermal changes occurred in rabbits when Oleth-10 or Oleth-20 were applied to abraded skin or under conditions of occlusive patch exposure.

Formulators should be aware that Oleths may increase permeability of the stratum corneum as demonstrated in in vitro studies.

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

In the absence of impurities data, the Panel cautioned that an Oleth preparation should not contain 1,4-dioxane or ethylene oxide which are possible oxidation products.

The Panel acknowledged the use of Oleths in hair sprays. However, based on particle size and cosmetic use concentrations, it was not considered that these ingredients, in formulation, are respirable. Thus, the Panel was not concerned by the lack of inhalation toxicity data, and considered the Oleth group to be safe for use in aerosolized products.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that Oleth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50 are safe in the present practices of use.

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[2]Available for review: Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036-4702, USA.