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Final Report on the Safety Assessment of Laneth-10 Acetate Group

The Laneths are ethoxylated lanolin alcohols that may be acetylated and used in a wide variety of cosmetic products. Acute oral toxicity studies indicate that Laneth-10 Acetate is relatively nontoxic to the rat; acute dermal toxicity studies indicate that it is relatively nontoxic to the guinea pig. Laneth-10 Acetate was found to be a mild, transient irritant to the rabbit's eye. Laneth-10 Acetate was shown to be nonirritating and nonsensitizing to 50 subjects.

Laneth-16 is slightly toxic when administered orally to the rat. Neither Laneth-16 nor Laneth-25 was a skin irritant or sensitizing agent in 50 subjects.

On the basis of the available animal data and limited human experience presented in this report, it is concluded that the Laneths are safe for topical application to humans in the present practices of use and concentration.

CHEMICAL AND PHYSICAL PROPERTIES

Structure

ETHOXYLATED lanolin alcohols comprise the Laneth series of cosmetic ingredients. Several members of the series are both ethoxylated and acetylated. The following Laneths are covered in this review:

1. Laneth-5
2. Laneth-16
3. Laneth-25
4. Laneth-9 Acetate
5. Laneth-10 Acetate

These five ingredients are all mixtures of alcohol ethers or alcohol ether-esters and will be referred to collectively as the Laneths or Laneth Acetates.

The alcohol ethoxylates (AE) are a group of mixtures related to the Laneths, and many of them have been tested for safety in a variety of animal and human studies. Information and data pertaining to the alcohol ethoxylates and to three additional Laneths (-15, -20, and -40) have been included here to permit a more complete appraisal of the safety of the five Laneths under review.

A related group of cosmetic ingredients, the Acetylated Lanolin Alcohols, has already been reviewed by CIR and determined by the Expert Panel to be safe at the concentrations presently used in cosmetic formulations.[1]

Lanolin is the secretory product of the sheep sebaceous gland, and upon saponification yields approximately 51% fatty acids and 47% alcohols.[2-7]

Lanolin alcohols (also referred to as wool alcohols or wool wax alcohols) are obtained by the hydrolysis of naturally occurring lanolin esters followed by the separation of lanolin acids. Lanolin alcohols are composed of approximately 25% long-chain aliphatic alcohols and 68% steroid alcohols.[1]

Laneth compounds are formed by reacting lanolin alcohols with ethylene oxide. The resulting product is a polyethylene ether. The molar ratio of the reactants, alcohol:ethylene oxide, can vary from 1:5 to 1:40. If this ratio is designated n, then Laneth-n is the reaction product of n moles of ethylene oxide for each mole of lanolin alcohol. The chemical composition of the three Laneth compounds used in cosmetics is reviewed below.

Laneth-5 is a polyethylene ether of lanolin alcohol and ethylene oxide.[8] It is produced by reacting an average of 5 moles of ethylene oxide per mole of lanolin alcohol.

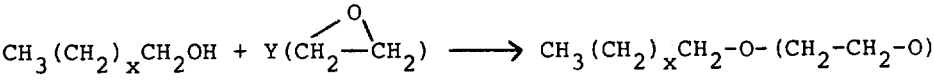
Similarly, Laneth-16 and Laneth-25 are polyethylene ethers produced by reacting an average of 16 and 25 moles, respectively, of ethylene oxide per mole of lanolin alcohol.[8]

Laneth Acetates, acetylated polyethylene ethers of lanolin alcohol, are formed by reacting ethoxylated lanolin alcohols with acetic anhydride. The reaction products are Laneths with acetylated terminal alcohol groups. Two Laneth Acetates are relevant to the cosmetics industry:

Laneth-9 Acetate is the completely acetylated polyoxyethylene ether of Laneth-9.[8]

Laneth-10 Acetate is the partially acetylated polyoxyethylene ether of Laneth-10.[8]

Alcohol ethoxylates are prepared by reacting ethylene oxide with primary aliphatic alcohols.[9] A generalized reaction is given below.

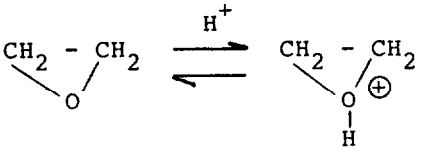


(alcohol) (ethylene oxide) (an alcohol ethoxylate)

Where: x varies from 6 to 16
y varies from 2.8 to 23

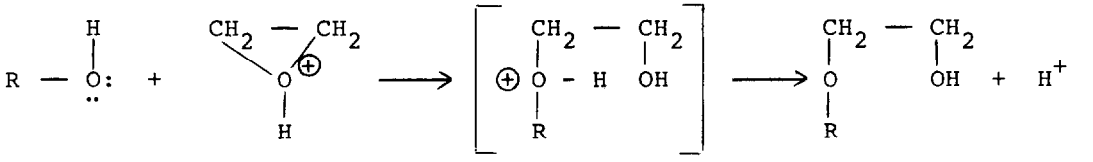
If primary dodecanol (lauryl alcohol or $CH_3(CH_2)_{10}CH_2OH$) were reacted, for example, with an average of nine moles of ethylene oxide per mole of alcohol, the resulting compound would be designated as $C_{12}AE_9$. Some tests have been conducted over a close range of alcohol ethoxylates, namely $C_{12\text{-}13}AE_{6.5}$ or $C_{14\text{-}15}AE_7$.

Ethylene oxide is an ether-like compound, and, as illustrated below, it can be converted to an oxonium-like ion (protonated epoxide) in the presence of acid.[10]



(ethylene oxide) (protonated epoxide)

This protonated epoxide can undergo nucleophilic attack by a variety of reagents. Alcohol ethoxylates result from the reaction of primary aliphatic alcohols with these oxonium-like ions. The reaction mechanism is detailed below.



(alcohol) (protonated epoxide) (intermediate) (alkoxy-alcohol or hydroxyether)

The reaction product is a bifunctional ether-alcohol. Since it does have a terminal alcoholic group, this compound can react in precisely this manner with additional ethylene oxide molecules until it ultimately forms the desired end product, a polyethoxy alcohol. The average number of ethylene oxide moieties incorporated in the polyether chain is determined by the original amount of ethylene oxide reacted. As is the case with Laneth-9 and -10 Acetates, the final polyethoxylate still has a terminal alcoholic group which can be acetylated.

Properties

Laneths are nongreasy, clear compounds which dissolve in water, alcohol, and some oils.[11] Ethoxylation increases the hydrophilic nature of the molecule; when the number of ethylene oxide moieties is increased, the polarity of the molecule becomes greater, so that its water solubility is enhanced. Laneth Acetates are soft, nontacky compounds which are soluble in water, alcohol, and oils. Acetylation decreases water solubility. Respecting this attribute, then, Laneth Acetates fall between the hydrophobic lanolin alcohols and the relatively hydrophilic Laneths.

Phase

Whereas Laneth compounds are either solids or liquids,[12] Laneth-9 and -10 Acetates are viscous liquids. The nonacetylated Laneths (-5, -15, -16, -25, and -40) range from soft to waxy solids; as the number of moieties of ethylene oxide increases, the relative hardness of the compound increases concurrently.

Solubility and Surface Tension

The Laneths are water-soluble surfactants whose physical properties vary with the amount of reacted ethylene oxide. There is a positive correlation between increased numbers of ethylene oxide moieties and increased surface activity. Critical micelle concentrations (cmc) obtained from surface-tension measurements for Laneths-16 and -40 and for Laneth-10 Acetate are 0.2%, 0.1%, and 0.2% weight, respectively. Additionally, as the molecular weight of the Laneth increases, the cmc decreases.[13]

Though the Laneths are classed as water-soluble agents, most of them have an aqueous solubility limited to 5–10% at 25°C.[13] Moreover, because true dissolution is not attained, these materials produce a transparent dispersion of colloid-sized particles in water.[14]

Conrad et al.[15] have reported that surface and interfacial tensions of Laneths-16 and -25 and for Laneth-9 and -10 Acetates increase with increased ethoxylation.

Specific Gravity and Viscosity

McCarthy and Schlossman[13] have reported that the specific gravity and viscosity of Laneths-16 and -40 and Laneth-10 Acetate decrease with decreasing Laneth concentration.

Wet and Flow Points

Laneths display pigment-dispersing properties in both aqueous and nonaqueous media. Wet-point data measure the amount of Laneth needed just to wet all of a given amount of pigment. Flow-point data measure the amount of Laneth required to assure even flow. In an aqueous medium, Laneth-16 and Laneth-9 and -10 Acetates were found to be effective wetting and dispersing agents for the four main groups of substances used in makeup cosmetics. However, neither the amount of ethoxylation nor the degree of acetylation produced any difference in wet and flow point measurements for the Laneth series.[15,16]

Reactivity

The Laneths and Laneth Acetates are efficient, primary nonionic emulsifiers which remain active in electrolytic solution; these ingredients remain relatively stable within the pH range of cosmetic formulations.[10] However, since the Laneths and Laneth Acetates contain some unsaturated components (aliphatic alcohols, sterols, and esters),[1] autoxidation or photolysis is possible during shelf life. The reaction products of such events remain unidentified, but peroxides and epoxides have been suggested.[17,18] Autoxidation can be inhibited by the addition of butylated hydroxytoluene (BHT) or α-tocopherol.

The main degradation products of the alcohol ethoxylates are the corresponding polyethylene glycols (PEG) and lanolin alcohols.[9] The PEGs will be covered extensively in subsequent reports.

Production

The extraction of lanolin alcohol from lanolin has been described elsewhere.[1,19] The resulting alcohols can be reacted with an appropriate molar concentration of ethylene oxide in an exothermic, addition reaction to generate the desired Laneth.[12] The lanolin alcohols are melted and then agitated in the presence of ethylene oxide gas at 130–180°C. Sodium methoxide may be used as a catalyst in this process.[14] Unreacted ethylene oxide is purged from the system. The product is refined by bleaching with hydrogen peroxide followed by vacuum stripping and filtration. Total acetylation of Laneth-9 results in the formation of Laneth-9 Acetate, while partial acetylation of Laneth-10 results in the formation of Laneth-10 Acetate.

Analytical Methods

Various quantitative methods for characterizing lanolin derivatives have been described.[20] These methods include iodine number, saponification number, moisture and volatility, ash (or residue) on ignition, acid number, and melting range. These procedures involve hydrolysis, fractionations, and chromatographic separations.[8]

A variety of physical, chemical, and physiochemical methods have been developed to define alcohol ethoxylates.[9]

Physical methods: foaming potential and surface tension changes are the two major physical techniques used to monitor levels of ethoxylated alcohols.

Chemical methods: most of these are based on the reactions of the ether oxygens of the alcohol ethoxylate. While the potassium iodobismuthate ($KBiI_4$) method has a sensitivity of approximately 0.01 mg/L, the limit of detection for the ammonium cobaltothiocyanate method is 0.1 mg/L. Other techniques include the phosphomolybdic acid, phosphotungstic acid, cholorosulfonic acid, and formaldehyde dinitrium salt methods. The last of these is highly sensitive, spectrophotometrically measuring concentrations as low as 1–10 ppm.

Physiochemical methods: thin-layer and paper chromatography have been used to separate and analyze alcohol ethoxylates. Because of the nonvolatile nature of most ethoxylates, gas chromatography has been employed to a lesser extent. A high-speed liquid-chromatography technique has also been reported.[9]

Natural Composition

Lanolin and all its derivatives are derived from sheep sebum, a complex mixture of organic compounds. The composition can vary considerably according to such variables as environment (for instance, diet and stress-mediated secretion of adrenocortical steroids) and the sex ratio of the animals used (that is, plasma differences in androgens and estrogens).[21] Whereas the glucocorticoids apparently inhibit the excretion of sebum, androgens not only stimulate it, but they also significantly alter the substance's chemical composition. Estrogens reduce sebum production. Overall, then, the sebaceous raw product containing lanolin can have a rather variable makeup. Lanolin and its derivatives may moreover be contaminated by small amounts of natural products.[1]

Impurities

The scouring of wool may introduce small amounts of detergent into lanolin extracts.[8] Laneth and Laneth Acetate preparations may contain ethylene oxide impurities that were not completely purged from the system. A reaction product of ethoxylation, 1,4-dioxane, may also be present in trace amounts; pertinent data are not available.[22] Traces of the sodium methoxide catalyst and its

degradation products may remain in the finished product.[14] Laneth Acetates may contain residual acetic acid. Antioxidants such as BHT and α-tocopherol may be present as stabilizing additives. Trace metals and pesticides from the fleece may also be found.[1]

USE

In addition to their extensive use in cosmetic formulations, lanolin derivatives are also used in a wide range of household and industrial products.

Purpose in Cosmetics

The Laneth compounds are used as emollients, nonionic emulsifiers, wetting agents, foam boosters and stabilizers, hair conditioners, solubilizers, cleansers, dispersing agents, and plasticizers.[11,13,14] They are found in some hair dressings, shampoos, hair dyes, hair rinses, cold wave solutions, creams, lotions, shaving creams, deodorants and antiperspirant sticks, creams, and solutions, after-shave lotions, colognes, hydrophilic ointments, liquid soaps, and bubble baths.[14,23] Laneth Acetates are also used in gels to control viscosity and as clarifying and moisturizing agents.[11,13]

Scope and Extent of Use in Cosmetics

The Laneths are used in cosmetic formulations at concentrations ranging from less than 0.1 up to 10%; Laneth Acetates are used at concentrations ranging from less than 0.1 up to 25%. These products, along with the approximate Laneth concentration used in them, are listed in Table 1.[24]

TABLE 1. PRODUCT FORMULATION DATA.[a]

Ingredient/Cosmetic Product Type	*Concentration (Percent)*	*No. of Product Formulations*
Laneth-10 Acetate		
Lotions, oils, powders, and creams	>0.1–1	2
Other baby products	>0.1–1	1
Bath oils, tablets, and salts	>0.1–1	6
Bubble baths	>1–5	1
	>0.1–1	2
Other bath preparations	>1–5	1
Eye shadow	>0.1–1	5
Colognes and toilet waters	>1–5	5
Perfumes	>10–25	1
	>5–10	1
Sachets	>1–5	1
Other fragrance preparations	>1–5	4
	>0.1–1	2
Hair conditioners	>1–5	3
	>0.1–1	1
Hair sprays (aerosol fixatives)	>0.1–1	17
	≤0.1	9
Rinses (noncoloring)	≤0.1	1
Shampoos (noncoloring)	>1–5	13
	>0.1–1	46
Permanent waves	>0.1–1	2
Tonics, dressings, and other hair grooming aids	>1–5	1
	>0.1–1	2
Wave sets	≤0.1	2
Other hair preparations	≤0.1	1

TABLE 1. (Continued).

Ingredient/Cosmetic Product Type	*Concentration (Percent)*	*No. of Product Formulations*
Blushers (all types)	>5–10	1
	>1–5	4
	>0.1–1	4
Face powders	>0.1–1	1
Foundations	>1–5	1
	>0.1–1	3
Makeup bases	>1–5	2
	>0.1–1	7
Other makeup preparations	>1–5	3
	>0.1–1	1
Nail creams and lotions	>1–5	1
Nail polish and enamel removers	>1–5	2
	>0.1–1	10
Other personal cleanliness products	>1–5	4
	>0.1–1	3
Aftershave lotions	>1–5	3
	>0.1–1	1
Shaving cream (aerosol, brushless, and lather)	>1–5	2
Other shaving preparations	>1–5	1
Cleansing (cold creams, cleansing lotions,	>5–10	1
liquids, and pads)	>1–5	3
	>0.1–1	2
Face, body, and hand (excluding shaving	>1–5	14
preparations)	>0.1–1	9
	≤0.1	2
Moisturizing	>1–5	4
	>0.1–1	2
Night	>1–5	1
Paste masks (mud packs)	>0.1–1	3
Skin fresheners	>0.1–1	3
Other skin care preparations	>1–5	3
Suntan gels, creams, and liquids	>1–5	1
Laneth-5		
Other fragrance preparations	>1–5	1
Hair conditioners	>1–5	1
Shampoos (noncoloring)	>1–5	1
Hair dyes and colors (all types requiring caution	>1–5	3
statement and patch test)	>0.1–1	28
Other makeup preparations	>1–5	1
Cleansing (cold creams, cleansing lotions,	>1–5	1
liquids, and pads)		
Face, body, and hand (excluding shaving	>5–10	1
preparations)	>0.1–1	2
Moisturizing	>1–5	1
	>0.1–1	4
Skin fresheners	>1–5	1
Other skin care preparations	>1–5	1
Laneth-16		
Bath oils, tablets, and salts	>1–5	1
Other bath preparations	>1–5	2
Sachets	>1–5	4
Other fragrance preparations	>0.1–1	1

TABLE 1. (Continued).

Ingredient/Cosmetic Product Type	*Concentration (Percent)*	*No. of Product Formulations*
Hair conditioners	>1–5	2
	>0.1–1	1
	≤0.1	1
Hair sprays (aerosol fixatives)	≤0.1	1
Permanent waves	>0.1–1	3
Shampoos (noncoloring)	>0.1–1	2
Tonics, dressings, and other hair grooming aids	>0.1–1	1
Wave sets	>0.1–1	1
Hair bleaches	>1–5	1
Blushers (all types)	>1–5	1
	>0.1–1	1
Deodorants (underarm)	>1–5	1
	>0.1–1	1
Other personal cleanliness products	>1–5	1
	>0.1–1	1
Aftershave lotions	>0.1–1	1
Face, body, and hand (excluding shaving preparations)	>0.1–1	2
Moisturizing	>1–5	6
	>0.1–1	1
Paste masks (mud packs)	>0.1–1	2
Laneth-25		
Bubble baths	>1–5	1
Sachets	>0.1–1	5
Hair conditioners	>1–5	1
Wave sets	>0.1–1	1
Blushers (all types)	>5–10	1
Laneth-9 Acetate		
Rinses (noncoloring)	>1–5	1
Other skin care preparations	>5–10	1
Aftershave lotions	>1–5	1

[a]From Ref. 24.

Potential Interactions with Other Ingredients

The Laneths can undergo autoxidation and photolysis. No data were available on chemical interactions with other ingredients.

Vehicles Commonly Used

The Laneths and Laneth Acetates display degrees of hydrophilicity and lipophilicity that vary according to their specific structures. Most are partially soluble in water, alcohols, and oils. Some are themselves used as vehicles for solubilization, dispersion, or emulsification of other cosmetic ingredients.

Surfaces to which Commonly Applied

Laneth-containing preparations can come into contact with the hair and scalp, hands, axillae, face, and skin in general.[11,14,23]

Frequency or Duration of Application

Because the range of Laneth-containing products is so wide, specific products must be addressed if we are to obtain meaningful information concerning frequency and duration of application. Frequency of application may vary from occasional to daily use. Duration of application can range from seconds to all day. The occasional or daily use may extend over a period of years.

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

Oral Administration

Rats receiving oral administration of ^{14}C-labeled (position of ^{14}C in molecule not given) alcohol ethoxylates (AE) excreted 54%, 26%, and 3% of the radioactivity in the urine, feces, and expired air (as $^{14}CO_2$), respectively, within 24 h. After 72 h, less than 4% of the label remained in the tissues of the animals.[9,25]

A single dose of ^{14}C-labeled $*C_{16}AE_9$ (label at carbon of alcohol moiety) was administered orally to rats on a normal diet and to rats on a diet containing 1% $C_{16-18}AE_9$ (13 weeks). At 72 h, the two groups showed no difference in the distribution of labeled excretory products. The primary route of ^{14}C elimination for each group was by way of $^{14}CO_2$ in the expired air. Of the total label expired, 60% was eliminated in the first 8 h. Significantly less label was excreted in the 0–8 h urine of the chronically fed group.[25]

Drotman[26] fed 25 mg (0.05–0.11 mCi, in 1 ml water) of radiolabeled AEs to rats. The AEs were ^{14}C-labeled either on the alkyl carbon adjacent to the polyethoxy chain, $*C_xAE_y$, or in the hydroxyl bearing position of the ethoxylate chain, C_xAE_y*. Excreta were collected for 72 h after dosing and analyzed for ^{14}C. The major portion of radioactivity from the AE-labeled compounds $C_{12}AE_6*$, $C_{13}AE_6*$, and $C_{14}AE_7*$ was found in the urine (52–55% of administered dose), with 23–27% in the feces and 2–3% in the expired air. There was no significant accumulation of label in the tissues. Similar results were obtained when the alkyl carbon-labeled compound, $*C_{12}AE_6$, was given per os in a single dose: urine (49%), feces (25%), and CO_2 (4%). Contrastingly, the distribution of excreted label differed greatly for two other AEs. Urine, feces, and CO_2 percentages of administered label were 45%, 13%, and 20%, respectively, for $*C_{13}AE_6$ and 12%, 8%, and 54%, respectively, for $*C_{15}AE_7$. Increasing the length of the alkyl chain and/or using odd-numbered carbon atom fatty alcohols increases the compound's tendency to be metabolized to $*CO_2$. The results of the studies on

TABLE 2. DISTRIBUTION OF LABEL 72 HOURS AFTER ORAL ADMINISTRATION TO RATS.[a]

	Percentage of administered dose					
	$C_{12}AE_6*$	$C_{13}AE_6*$	$C_{14}AE_7*$	$*C_{12}AE_6$	$*C_{13}AE_6$	$*C_{15}AE_7$
Liver	0.5	0.3	0.4	0.3	0.6	1.1
G.I. wash	0.8	0.6	0.4	0.8	1.1	0.2
G.I. tract	0.1	0.1	0.1	0.2	0.4	1.0
Urine	52.1	53.9	54.9	48.7	45.1	12.3
Feces	27.0	25.6	22.7	25.4	13.3	7.9
CO_2	3.2	2.4	1.9	3.6	20.4	53.7
Carcass	1.7	1.9	2.7	9.3	5.0	9.2
Cage wash	2.4	1.9	2.9	2.6	2.2	3.0
Recovery	87.8	86.7	86.0	90.9	88.1	88.4

[a]Modified from Ref. 26.

TABLE 3. DISTRIBUTION OF LABEL 144 HOURS AFTER ORAL ADMINISTRATION TO HUMANS.[a]

	Percentage of administered dose			
	$*C_{12}AE_6$	$C_{12}AE_6*$	$*C_{13}AE_6$	$C_{13}AE_6*$
Urine	75.4	78.5	63.1	80.8
Feces	4.0	5.7	6.9	3.8
CO_2	3.0	4.8	13.3	3.8
Recovery	82.4	89.0	83.3	88.4

[a]Modified from Ref. 26.

the distribution and excretion of the ^{14}C-labeled compounds are summarized in Table 2. Information is not presented as to the chemical nature of any metabolite other than CO_2.[26]

Similar results were obtained in collateral human studies in which a single dose of 50 mg (0.185–0.215 mCi) of labeled AE (in orange juice) was administered orally. For $C_{12}AE_6*$ and $C_{13}AE_6*$ respective amounts of recovered label in the 144-hour urine, feces, and CO_2 were 79% and 81%, 6% and 4%, and 5% and 4% of administered ^{14}C. For $*C_{12}AE_6$ and $*C_{13}AE_6$, the corresponding values were 75% and 63% (urine), 4% and 7% (feces), and 3% and 13% (CO_2) (Table 3).[26] Blood levels of radioactivity peaked at 1.3 to 1.7 μg AE/g blood at 1–2 hours after dosing (Table 4).[26]

Dermal Administration

Percutaneous penetration of ^{14}C-AE_n was studied in adult and weanling guinea pigs and rats. Serum levels of ^{14}C were found to be twice as high in young as compared with adult guinea pigs. In the rat study no age-related differences were observed.[27]

The distribution of topically applied ^{14}C-labeled alcohol ethoxylates (12.5 mg/kg) was monitored in the rat. After 72 h, 29%, 8%, 11%, and 40% of the label which had been applied to the shaved dorsum of the animals was recovered in the urine, feces, respired air, and tissues, respectively.[9,28]

Drotman[26] applied 0.5 mg (about 2 mCi) of $C_{12}AE_6*$, $C_{13}AE_6*$, or $C_{14}AE_7*$ to the rat skin within a 20-cm^2 area on the back. For the three AEs, the 72-hour distribution of label was 60%, 44%, and 60% (not absorbed but remaining at the application site), 25%, 15%, and 16% (urine), 3%, 5%, and 5% (feces), and 3%, 2%, and 2% (CO_2), respectively. Corresponding values for $*C_{12}AE_6$, $*C_{13}AE_6$, and $*C_{15}AE_7$ were 42%, 42%, and 47% (application site), and 23%, 21%, and 6% (urine),

TABLE 4. BLOOD LEVELS[a] OF LABELED ETHOXYLATE.[b]

Hours after dosing	$*C_{12}AE_6$	$C_{12}AE_6*$	$*C_{13}AE_6$	$C_{13}AE_6*$
0.5	1.0	1.5	1.4	1.4
1.0	1.3	1.7	1.4	1.4
1.5	1.2	1.6	1.2	1.3
2	1.0	1.3	1.0	1.2
4	0.8	0.8	0.7	0.7
6	0.5	0.5	0.4	0.5
8	0.4	0.4	0.3	0.4
12	0.2	0.3	0.2	0.2
144	0.1	0.1	0.0	0.1
No. of Subjects	5	5	4	5

[a]μg AE/g blood.
[b]Modified from Ref. 26.

TABLE 5. DISTRIBUTION OF LABEL 72 HOURS AFTER DERMAL APPLICATION TO RATS.[a]

	Percentage of administered dose					
	$C_{12}AE_6$*	$C_{13}AE_6$*	$C_{14}AE_7$*	*$C_{12}AE_6$	*$C_{13}AE_6$	*$C_{15}AE_7$
Liver	0.4	0.4	0.2	0.4	0.4	0.5
Skin	1.4	7.0	3.6	3.2	1.6	1.4
Application site	59.7	43.6	59.9	41.7	42.4	47.1
Urine	24.8	15.1	16.1	23.4	21.1	6.4
Feces	3.4	4.9	5.4	6.2	6.4	1.8
CO_2	3.4	2.3	2.4	4.2	9.1	21.7
Carcass	5.0	8.2	9.9	6.4	6.7	9.3
Cage wash	2.5	17.5	6.6	3.9	3.2	6.2
Recovery	100.6	99.0	104.1	89.4	90.9	94.4

[a]Modified from Ref. 26.

6%, 6%, and 2% (feces), and 4%, 9%, and 22% (CO_2), respectively (Table 5). This study clearly indicates a slow absorption of the alcohol ethoxylates (40–60% in 72 h) through the rat skin.

Similar studies were conducted in humans; for 8 h under nonocclusive conditions, 100 mg (about 100 μCi) of $C_{12}AE_6$* were applied to a 90-cm^2 area of the forearm. Most of the label was not absorbed and remained at the application site (70% after 144 h); 1–2% was found in the 144-h urine and none was found in the feces or expired CO_2. Labeled ^{14}C was barely detectable in the blood (0.14 μg/g maximum).[26]

General Effects

Anesthetic-Analgesic Effects

Several alcohol ethoxylates display topical anesthetic or intralesional analgesic properties.

Topical anesthesia

Aqueous solutions of 0.5% $C_{12}AE_9$, 1.0% $C_{12}AE_{7\text{-}13}$, and 1.0% $C_{12}AE_{11\text{-}9}$ are effective surface anesthetics to the rabbit cornea.[27,29] Several AE_9 compounds ($C_{1,\ 2,\ 3,\ 4,\ 6,\ 8,\ 10,\ 12}$ and $_{14}$) have also been applied to the rabbit cornea. The $C_{1,\ 2,\ 3}$ and $_4$ homologs showed no anesthetic effect. The longer chain compounds did display an effect. It was found that the longer the hydrocarbon chain the greater the intensity of the anesthetic effect.[30]

Intralesional analgesia

Stellmach and associates[31] evaluated the local analgesic effect of a 2% solution of $C_{12}AE_9$ injected into the infraorbital nerve canal in several dogs with silver electrodes implanted in their canine teeth. Pain threshold values were obtained following application of electrical stimuli. In the presence of the ethoxylated alcohol, the threshold to pain increased an average of 19-fold.

Anticonvulsant Activity

Mice were fed orally or injected subcutaneously with $C_{12}AE$. Oral administration (dose unspecified) produced no anticonvulsant effect. After near neurotoxic doses (75–110 mg/kg subcutaneous), weak anticonvulsant activity was observed.[32]

Hemolytic Activity

Several alcohol ethoxylates, $C_{12}AE_{6,\ 7}$ and $_8$ have an in vitro hemolytic effect on canine blood. This action appears to be affected by a number of factors. The AE concentration needed to produce hemolysis is directly related to the erythrocyte concentration. Hemolytic activity decreases as the chain length of the ethoxylate increases. Hemolytic activity increases with increased temperature due to greater AE adsorption to the erythrocyte surface and to increased release of lipid from the RBC plasma membrane.[33]

Effect on Hemostasis

Rabbits injected subcutaneously with $C_{12}AE_{11.9}$ at 14 mg/kg daily for five days, showed no abnormal extension of coagulation time.[34]

Lanolin Allergy

Wool alcohols, precursors of the Laneths, are responsible for most lanolin allergy.[1] The greatest allergic reaction is to the C_{14}–C_{16} components of the alcohol.[35] The North American Contact Dermatitis Group[36] evaluated a group of 1,996 patients with contact dermatitis; 1% of the females and 2% of the males were found to be allergic to wool alcohols (30% in petrolatum). A study in Europe estimates the incidence of lanolin allergy in the general population to be no more than 9.7 per million people.[37] Still, removal of free fatty alcohols from lanolin results in a 96 percent reduction in hypersensitivity reactions.[38]

Laneth-10 Acetate

Animal Toxicity

Acute Oral: Four groups of 10 rats each were given Laneth-10 Acetate by gavage. The dose range used in the study was 30–60 ml/kg. The oral LD50 was reported to be 41.8 ml/kg[39] (Table 6). Other reported acute oral LD50 values for Laneth-10 Acetate are >5 g/kg[40] and >64 ml/kg.[39]

Dermal Toxicity: An unspecified number of guinea pigs was exposed to Laneth-10 Acetate for 24 h. The percutaneous LD50 was estimated to be >3.0 g/kg[40] (Table 6).

TABLE 6. ANIMAL STUDIES ON LANETH-10 ACETATE.

Test	*No. and species of animals*	*Dose/ Treatment*	*LD50/PII*	*Ocular Irritation Scores (110 max.) Days* 1	2	3	4	7	*Ref.*
Acute									
Oral toxicity	Rats (M/F) 4 groups of 10	30–60 ml/kg	41.8 ml/kg	–	–	–	–	–	39
	Rats (M/F) 6 groups of 5	2–64 ml/kg	>64 ml/kg	–	–	–	–	–	39
	Rats	–	>5 g/kg	–	–	–	–	–	40
Dermal irritation	6 Rabbits	Undiluted	0.0/8.0	–	–	–	–	–	42
	6 (M/F)	Undiluted	0.6/8.0	–	–	–	–	–	39
	6 (3M/3F)	Undiluted	0.75/8.0	–	–	–	–	–	41
Dermal corrosion	6 Rabbits (3M/3F)	Undiluted	No corrosion or irritation	– –	– –	– –	– –	– –	39
Dermal toxicity	Guinea Pigs	24 h contact	>3.0 g/kg	–	–	–	–	–	40
Ocular irritation	3 Rabbits, unwashed eyes	Undiluted	–	0.0	–	–	–	–	42
	3 Rabbits, washed after 2 sec	Undiluted	–	0.0	–	–	–	–	42
	3 Rabbits, washed after 4 sec	Undiluted	–	0.0	–	–	–	–	42
	6 Rabbits, unwashed eyes	Undiluted	–	2.3	0.3	0.3	–	0.0	39

Skin Irritation: In three tests undiluted Laneth-10 Acetate was evaluated as a potential irritant to the rabbit skin. The FHSA procedure using six rabbits/group was employed. The Primary Irritation Index (PII) values ranged from 0.0 to 0.75 out of a maximum of 8[39,41,42] (Table 6).

Dermal Corrosion: Six rabbits were exposed for four hours to undiluted Laneth-10 Acetate in a DOT dermal corrosion test. No irritation or corrosion was reported[39] (Table 6).

Ocular Irritation: Undiluted Laneth-10 Acetate was instilled into one eye of each of nine rabbits. All irritation scores for both unwashed and washed eyes were 0.0.[42] In a similar study using six rabbits with eyes unwashed following instillation, the irritation scores were 2.3, 0.3, 0.3, and 0.0 for Days 1, 2, 3, and 7, respectively[39] (Table 6).

Clinical Assessment of Safety

Primary Skin Irritation: Laneth-10 Acetate was evaluated as a potential skin irritant. Twenty-one subjects underwent a single insult occluded patch test. Four percent Laneth-10 Acetate was dispersed in alcohol, applied to the test area, and the vehicle permitted to evaporate before the patch was applied. The test areas were scored at 24 h. Since no erythematous reactions were produced in response to it, the ingredient was adjudged to have a low level of primary skin irritation potential.[2,40]

Skin Irritation and Sensitization: Repeated insult occluded patch tests were carried out on Laneth-10 Acetate. Human subjects were divided into five groups of 10 to 12 each. In preliminary tests, the ingredient was tested at five different aqueous dispersion levels (10%, 20%, 30%, 40%, or 50%). Approximately 0.1 ml/cm^2 of test sample was applied four times and the results scored. From these initial tests, one concentration (50%) was selected for the actual test on the 50 volunteers. Test sites were exposed to sample for four consecutive days, read on the fifth day, and rested the next two days. This protocol was repeated three times and followed up by a 15-day rest period. At this time, 24-hour occluded challenge exposures were made at new sites and evaluated for immediate hypersensitivity reactions. Twenty-four, 48, and 72 h later evaluations for delayed hypersensitivity reactions were made at the new sites. Laneth-10 Acetate produced no primary irritation after the initial exposure. Exposures 2–12 demonstrated that this ingredient is not a "fatiguing" agent. ("Fatiguing" ability involved potential cumulative effects due to repeated applications of sample.)[43] Upon challenge, no adverse reactions were reported. Laneth-10 Acetate is not a skin irritant or sensitizing agent.[39]

A facial mask containing 1% Laneth-10 Acetate was tested on 200 subjects using the repeated insult patch test. A total of 15 applications per person were made and followed by a challenge exposure. No primary irritation was observed after the first application. For applications 2–15, 6% of the volunteers displayed visible skin changes as the result of "fatiguing." Challenge applications caused no skin sensitization.[44] Water-tight coverings of the facial mask type tend to increase percutaneous absorption of water-soluble materials.[45] This effect is caused, in part, by increased skin hydration from lower lying structures; in part by lack of evaporation from the skin surface; and in part by increased temperature. Even though it may have such an effect on percutaneous absorption, the facial mask was found to be relatively innocuous.

Laneth-9 Acetate

Animal Toxicity

Acute Oral: Five groups of two rats each were given Laneth-9 Acetate by gastric intubation. The dose range studied was 2.5 to 40 ml/kg. The oral LD50 was said to be in excess of 10 ml/kg.[39] (Table 7).

Skin Irritation: A 20% aqueous preparation of Laneth-9 Acetate was used on three rabbits in a FHSA skin irritation study. The PII value was recorded as 0.8[39] In another experiment, undiluted sample was applied to the rabbit skin. The PII score was 0.65.[39] (Table 7).

Dermal Corrosion: Three male and three female rabbits were used in a DOT dermal corrosion test with undiluted Laneth-9 Acetate. No irritation or corrosion was reported.[39] (Table 7).

Ocular Irritation: A 20% aqueous preparation of Laneth-9 Acetate was instilled into one eye of each of three rabbits. At Days 1, 2, and 3 the resulting scores were, respectively, 2.0, 0.6, and 0.0.[39]

TABLE 7. ANIMAL STUDIES ON LANETH-9 ACETATE.[a]

Test	No. and species of animals	Dose/Treatment	LD50/PII	Ocular Irritation Scores (110 max.) Days 1	2	3	4	7
Acute								
Oral toxicity	Rats (M/F) 5 groups of 2	2.5–40 ml/kg	>10 ml/kg (No deaths)	–	–	–	–	–
Dermal irritation	3 Rabbits	20% in water	0.8/8.0	–	–	–	–	–
	6 (M/F)	Undiluted	0.65/8.0	–	–	–	–	–
Dermal corrosion	6 Rabbits (3M/3F)	Undiluted	No corrosion or irritation	–	–	–	–	–
Ocular irritation	3 Rabbits, unwashed eyes	20% in water	–	2.0	0.6	0.0	–	–
	6 Rabbits, unwashed eyes	Undiluted	–	3.7	3.7	2.0	–	0.3

[a]From Ref. 39.

Undiluted sample was used in six rabbits; their respective scores were 3.7, 3.7, 2.0, and 0.3 for Days 1, 2, 3, and 7.[39] (Table 7).

Clinical Assessment of Safety

Skin Irritation and Sensitization: Laneth-9 Acetate (50%) was used on 50 subjects in a repeated insult occluded patch test according to the procedure described above.[39] It was concluded that Laneth-9 Acetate is neither a primary skin irritant nor a sensitizer. Following exposures 2–12, several irritation reactions were noted; this result indicates that the ingredient under consideration may be a mild "fatiguing" agent.[39]

Laneth-5

Animal Toxicity

Acute Oral: Seven groups of five rats each were given Laneth-5 by gavage in doses ranging from 4 to 48 ml/kg. The oral LD50 was recorded as 25.9 ml/kg.[42] In a different study, four groups of five rats each were given Laneth-5 at a dosage of 25–64 ml/kg. The resulting oral LD50 was 45.0 ml/kg.[39] (Table 8).

Skin Irritation: In a skin irritation study a 10% solution of Laneth-5 in mineral oil was used on three rabbits; the resulting PII was 0.5. The PII produced by undiluted sample used on six rabbits was 0.8.[39] In a similar study of six rabbits, undiluted Laneth-5 produced a dermal PII of 1.3.[42] (Table 8).

Dermal Corrosion: A DOT dermal corrosion test using undiluted Laneth-5 was run on six rabbits. No irritation or corrosion was reported.[39] (Table 8).

Ocular Irritation: A 10% solution of Laneth-5 in mineral oil was instilled into one eye of each of three rabbits. All scores were 0.0 for Days 1, 2, 3, 4, and 7. When undiluted sample was used instead, the scores were 2.7, 2.3, 2.0, and 0.0 at Days 1, 2, 3, and 7, respectively.[39] In another test undiluted sample was instilled into one eye of each of nine rabbits. All resulting scores were 0.0[42] (Table 8).

Clinical Assessment of Safety

Skin Irritation and Sensitization: Laneth-5 (50%) was administered to 50 subjects in a repeated insult occluded patch test according to the procedure described above.[39] It was concluded that

TABLE 8. ANIMAL STUDIES ON LANETH-5.

Test	No. and species of animals	Dose/ Treatment	LD50/PII	Ocular Irritation Scores (110 max.) Days 1	2	3	4	7	Ref.
Acute									
Oral toxicity	Rats (M/F) 7 groups of 5	4–48 ml/kg	25.9 ml/kg	–	–	–	–	–	42
	Rats 4 groups of 5	25–64 ml/kg	45.0 ml/kg	–	–	–	–	–	39
Dermal irritation	3 Rabbits	10% in mineral oil	0.5/8.0	–	–	–	–	–	39
	6 (M/F)	Undiluted	0.8/8.0	–	–	–	–	–	39
	6 (M/F)	Undiluted	1.3/8.0	–	–	–	–	–	42
Dermal corrosion	6 Rabbits (3M/3F)	Undiluted	No corrosion or irritation	–	–	–	–	–	39
Ocular irritation	3 Rabbits, unwashed eyes	10% in mineral oil	–	0.0	0.0	0.0	0.0	0.0	39
	6 Rabbits, unwashed eyes	Undiluted	–	2.7	2.3	2.0	–	0.0	39
	3 Rabbits, unwashed eyes	Undiluted	–	0.0	–	–	–	–	42
	3 Rabbits, washed after 2 sec	Undiluted	–	0.0	–	–	–	–	
	3 Rabbits, washed after 4 sec	Undiluted	–	0.0	–	–	–	–	

Laneth-5 neither produces primary irritation nor elicits hypersensitivity reactions. Applications 2–12 did indicate, though, that it is a mild "fatiguing" agent.[39]

Laneth-16

Animal Toxicity

Acute Oral: Eight groups of five rats each were given Laneth-16 via gastric intubation over a dosage range of 4–64 ml/kg. The oral LD50 was recorded as 9.33 ml/kg.[42] In a similar study on six groups of five rats each, a dosage range of 4–32 ml/kg was employed. The resultant LD50 was 12.2 ml/kg.[37] Five groups of five rats each were exposed to Laneth-16 at a dose ranging from 1.25 to 20.0 g/kg. The oral LD50 was reported to be in excess of 2.15 g/kg.[39] (Tables 9 and 10).

Skin Irritation: In skin irritation studies, three rabbits were exposed to a 10% aqueous solution of Laneth-16 and six rabbits to undiluted sample. The resulting PII values were given as 1.0 and 2.43, respectively.[39] In two similar tests of three rabbits each, use of undiluted sample resulted in PII scores of 1.25 and 1.0.[42] (Tables 9 and 10).

Dermal Corrosion: A DOT dermal corrosion test using undiluted Laneth-16 was carried out on six rabbits. No irritation or corrosion was found.[39] (Tables 9 and 10).

Ocular Irritation: Undiluted Laneth-16 was instilled into one eye of each of nine rabbits (eyes unwashed in three, washed in six). The 24-hour scores were 1.3 and 0.0 for the rabbits with eyes unwashed and washed, respectively. In a similar experiment, the scores were reported to be 10.7 and

TABLE 9. ANIMAL STUDIES ON LANETH-16.

Test	No. and species of animals	Dose/ Treatment	LD50/PII	Ocular Irritation Scores (110 max.) Days 1	2	3	4	7	Ref.
Acute									
Oral toxicity	Rats (M/F) 8 groups of 5	4–64 ml/kg	9.33 ml/kg	–	–	–	–	–	42
	Rats (M/F) 6 groups of 5	4–32 ml/kg	12.2 ml/kg	–	–	–	–	–	42
	Rats 5 groups of 5	1.25–20.0 g/kg Administered in 50 percent corn oil	>2.15 g/kg	–	–	–	–	–	39
Dermal irritation	3 Rabbits	10 percent in water	1.0/8.0	–	–	–	–	–	39
	6 (M/F)	Undiluted	2.43/8.0	–	–	–	–	–	39
	3 (M/F)	Undiluted	1.25/8.0	–	–	–	–	–	42
	3 (M/F)	Undiluted	1.0/8.0	–	–	–	–	–	42
Dermal corrosion	6 Rabbits (3M/3F)	Undiluted	0.0/8.0	–	–	–	–	–	39
Ocular irritation[a]	3 Rabbits, unwashed eyes	Undiluted	–	1.3	–	–	–	–	42
	3 Rabbits, washed after 2 sec	Undiluted	–	0.0	–	–	–	–	
	3 Rabbits, washed after 4 sec	Undiluted	–	0.0	–	–	–	–	
	3 Rabbits, unwashed eyes	Undiluted	–	10.7	–	–	–	–	
	3 Rabbits, washed after 2 sec	Undiluted	–	0.0	–	–	–	–	42
	3 Rabbits, washed after 4 sec	Undiluted	–	0.0	–	–	–	–	
	6 Rabbits, unwashed eyes	Undiluted	–	9.0	7.0	5.0	4.8	0.8	39
	3 Rabbits, washed after 4 sec	Undiluted	–	7.3	4.3	2.7	0.0	0.0	

[a]See also Table 6.

0.0.[42] A third study using undiluted sample on nine rabbits (eye unwashed in six, washed after four seconds in three) produced ocular scores of 9.0, 7.0, 5.0, 4.8, and 0.8 for Days 1, 2, 3, 4, and 7, respectively (unwashed eyes) and 7.3, 4.3, 2.7, 0.0, and 0.0 (washed eyes) for the same times.[39] (Tables 9 and 10).

TABLE 10. RABBIT EYE IRRITATION TESTS.[a]

Shampoo used	*Shampoo A*				*Shampoo A*[b]				*Shampoo B*			*Shampoo B*[b]			*Shampoo C*				*Shampoo C*[b]			
Hours after appl.	4	24	48	72	4	24	48	72	4	24	48	4	24	48	4	24	48	72	4	24	48	72
No. of rabbits	4	4	4	4	4	4	4	4	8	8	8	8	8	8	6	6	6	6	6	6	6	6
Average score (Max. score = 110)	14	7	2	0	3	1	0	0	11	1	0	4	0	0	17	11	2	0	14	5	1	0

[a]Adapted from Ref. 48.
[b]With 35 percent Laneth-16 Additive.

Russell and Hoch[46] and Hoch and Russell[47,48] conducted eye irritation studies in rabbits on shampoos with and without Laneth additives. They employed a modified Draize test in which the members of each pair of test samples (with or without Laneth additive) were tested simultaneously, instilling one formulation into one eye of a test animal and the second into the other eye. Laneth-16 was added to facilitate the incorporation (solubilization) of lanolin oil into the three shampoos. Samples with Laneth-16 additive showed reduced eye irritation (Table 10).[48] The mechanism of this reduction was further investigated. The guinea pig blink reflex test was used to determine whether Laneth-16 produces an anesthetic effect on the eye; it does not.

Clinical Assessment of Safety

Skin Irritation and Sensitization: Fifty human subjects were exposed to 50% Laneth-16 in repeated insult occluded patch tests as described above.[39] It was concluded that Laneth-16 did not cause visible evidence of irritation either after application 1 or when it was used as a challenge allergen at application 13. For applications 5–12, Laneth-16 was a "fatiguing" agent in one subject.[39]

Eye Irritation: Hoch and Russell[48] have demonstrated that Laneth-16 can reduce the eye irritation associated with several shampoo preparations. In an initial study, the authors and colleagues tested the shampoos on themselves; they used three different shampoos with and without Laneth-16 additive. Capillary pipettes were used to instill approximately 0.02 ml of concentrated sample into the everted lower orbital sacs. The tests were conducted in pairs: the sample without Laneth-16 in one eye and the sample with Laneth-16 in the other. In all cases, the preparation without additive was found to be quite irritating; it caused excessive tearing for several minutes, pain for an hour, and eye redness for several hours. On the other hand, the sample containing additive caused only a very weak response of transient discomfort without associated redness.

These authors also tested a simulated commercial children's shampoo formulation. They simultaneously tested this formulation, and the same one with 3.5 percent Laneth-16 additive. The tests were conducted several times on groups of 10 men. The full strength formulations without Laneth caused burning, tearing, and stinging of the eyes for up to an hour. The concentrated formulation with additive caused only weak burning and stinging which subsided after 10–20 min.[48]

Laneth-25

Animal Toxicity

Acute Oral: Five groups of five rats each were given Laneth-25 by gavage. Sample was administered in 50% corn oil over a dosage range of 1.25 to 5.0 g/kg. The resulting oral LD50 was found to be in excess of 3.0 g/kg.[39] (Table 11).

Skin Irritation: A group of six rabbits was exposed to undiluted Laneth-25 in a Draize skin irritation study. A second group of six rabbits was exposed, according to the Draize procedure, to a 10% aqueous preparation of the ingredient. The corresponding PII values were 3.83 and 0.04, respectively.[39] (Table 11).

Ocular Irritation: Undiluted Laneth-25 was instilled into one eye of each of six rabbits, and there was no subsequent rinsing of the eye. The 1-, 2-, 3-, and 7-day ocular scores were reported as 5.3, 4.7, 2.7, and 1.3, respectively.[39] (Table 11).

Clinical Assessment of Safety

Skin Irritation and Sensitization: Fifty subjects were administered 50% Laneth-25 in repeated insult occluded patch tests as described above.[39] Laneth-25 was found to be a nonirritating, "nonfatiguing," nonsensitizing agent.[39]

Alcohol Ethoxylates

The alcohol ethoxylates are mixtures of compounds closely related to the Laneths; polyethylene glycols (PEG) are primary degradation products of the Laneths. When administered orally to rabbits, mice, rats, and guinea pigs, PEGs were found to be relatively innocuous. The acute oral LD50s

TABLE 11. ANIMAL STUDIES ON LANETH-25[a]

Test	No. and species of animals	Dose/Treatment	LD50/PII	Ocular Irritation Scores (110 max.) Days 1	2	3	4	7
Acute								
Oral Toxicity	Rats 5 groups of 5	1.25–5 g/kg Administered in 50% corn oil	>3.0 g/kg	–	–	–	–	–
Dermal	6 Rabbits	10% in water	0.04/8.0	–	–	–	–	–
irritation	6 Rabbits	Undiluted	3.83/8.0	–	–	–	–	–
Ocular Irritation	6 Rabbits, unwashed eyes	Undiluted	–	5.3	4.7	2.7	–	1.3

[a]From Ref. 39.

for PEGs 200–1000 ranged from 16 to 44 g/kg.[64] When given per os, painted on the skin, or injected subcutaneously, PEGs do not induce tumors in mice, rats, guinea pigs, or dogs.[49]

Animal Toxicity: General Studies

Inhalation toxicity

Rats were exposed to aerosol preparations of $C_{12\text{-}13}AE_{6.5}$ or $C_{14\text{-}15}AE_7$ for 4 h; LC50 values were determined to be between 1.5 and 3.0 mg/L for both materials.[27]

Nine rats were subjected to a 20% aqueous aerosol preparation of $C_{12}AE_7$ for 2 h/day for 10 days. Two animals had mild laryngeal irritations; the rest showed no adverse effects from the inhalation regimen.[50]

Grubb et al.[50] studied the potential toxicity of $C_{12}AE_7$ on ciliary movement in rat tracheal ring preparations. No inhibition was found at an aqueous concentration of 20 mg/L; at concentrations of 50 mg/L, ciliary activity was reduced, and at 500 mg/L it was completely inhibited.

Oral toxicity

Several alcohol ethoxylates have been fed to rats and have had little adverse effect. Up to 1.18% $C_{12}AE_7$ was included in the diet of rats for four weeks. No reaction was noted.[51] Rats were fed $C_{12}AE_9$ (up to 780 mg/kg/day) for 22 days with no major deleterious effects noted. Rats were fed $C_{12}AE_9$ (up to 1.95 g/kg/day) for five days. The LD50 was approximately 1.2 g/kg/day over the five-day period.[52,53]

$C_{12}AE_9$ was administered orally to rats in a 15% aerosol formulation; five-day LD50 values for 0.2 and 1.28 g/kg were 0.1 and 6.4 ml/kg/day, respectively.

No indication of toxicity was reported for the daily feeding of 0.05% $C_{12\text{-}13}AE_{6.5}$ to rats for three months. Higher doses (0.1%, 0.5%, and 1.0%) caused decreases in growth, both weight, and overall food consumption, possibly due to the decreased palatability of the food with increased ethoxylation. $C_{14\text{-}15}AE_7$ (0.1%, 0.5%, and 1.0%) was also fed to rats for three months; no toxic effects were observed.[27]

Mucosal irritation

$C_{12}AE_9$ (5 ml, undiluted) was applied once to the cervical and vaginal mucosa in dogs. No adverse irritation effects were observed.[52,53]

Canine vaginal and cervical mucosa exposed to $C_{12}AE_9$ (15% aqueous preparation, 5 ml volume) five days per week for two weeks showed no irritation. This compound, in an aerosol cream (15% aqueous preparation, 10 ml volume), was similarly applied to another group of dogs three days per week for six months. There were no adverse mucosal effects.[52,53]

Skin irritation and sensitization

Repeated topical application of $C_{12}AE_7$ or $C_{12}AE_9$ induced little skin irritation in the rabbit.[50,52] Two percutaneous tests (4 and 13 weeks) using $C_{12-13}AE_{6.5}$ or $C_{14-15}AE_7$, both at 50 mg/kg/day applied 5 days/week, were conducted on rabbits; the skin was abraded in the shorter test but left intact in the longer one. The C_{12} and C_{14} compounds caused slight to moderate and moderate to severe skin irritation, respectively, for both test periods. The skin was not sensitized.[27]

Intramuscular Toxicity: Various C_{12} and C_{16} alcohol ethoxylates at 1 or 5 percent in saline solution were injected into the hind leg muscles of rabbits. The degree of local irritation correlated directly with sample concentration and with frequency of injection. Increased ethoxylation decreased reactivity.[54]

Spermicidal Activity: Several investigators have shown that some of the alcohol ethoxylates display spermicidal or sperm immobilization properties; these include C_8AE_7 (0.06–0.125%), $C_{12}AE_{19-23}$ (0.03–0.06%), $C_{16}AE_{19-23}$ (0.03–0.06%) and $C_{12}AE_9$ (0.033–0.083%). C_6AE_4 (0.5%) is not a spermicidal agent.[52,55]

Special Studies: Teratology

Twenty-five pregnant rabbits per group were fed $C_{12}AE_6$ (0, 50, 100, or 200 mg/kg/day) from Days 2 to 16 of the gestation period. On day 28 the fetuses were removed by post-mortem, caesarean section. No teratogenic effects were observed in any of the fetuses. The latter two doses did cause an increase in maternal toxicity: 16% (100 mg group) and 40% (200 mg group) of the rabbits showed ataxia and/or loss of righting reflex. There was some weight loss in the 200 mg group.[9,28]

Multiple generation

Several two-generation reproduction studies have been conducted. No alcohol ethoxylate-mediated reproductive effects were seen. In one study, female rats were fed 0%, 0.05%, 0.1%, or 0.5% $C_{14-15}AE_7$ either continuously or from days 6 to 15 of the gestation period; there was no adverse effect in any parental or progeny group. Fertility, gestation, and viability indices were not different from control values. A similar study using $C_{12}AE_6$ was carried out with the same result: no compound-related reproduction abnormalities.[9,28]

Mutagenesis

Several of the AE_6 compounds were tested for mutagenicity. Male mice were fed 20, 100, or 200 mg/kg of AE_6 subacutely or 100, 500, or 1000 mg/kg acutely. For the dominant lethal assay, no changes in the mutagenic indices were found. In an in vivo study, hamsters were fed 80, 400, or 800 mg/kg of AE_6 and then sacrificed at 6, 24, or 48 h. Bone marrow cells were scanned for chromosomal anomalies, with none being noted. In an in vitro study, human leukocytes were incubated with 2, 20, or 100 μg/ml of AE_6 for 18, 24, or 48 h. No chromosomal abnormalities were observed.[9,28]

Clinical Assessment of Safety

Inhalation toxicity

Sixteen volunteers were continuously exposed for 8 h to the vapor phase of aqueous solutions of $C_{12}AE_7$. No toxic effects were reported.[56]

Larkin[56] used a $C_{12}AE_7$-containing preparation in the treatment of respiratory tract diseases. Ninety-two children inhaled the vapors of this preparation continuously for 8 h. Therapeutic results indicated a substantial improvement of symptoms; there were no adverse responses involving intolerance or irritation. The inhalant product is currently on the market and in use today.

Mucosal irritation

Berberian et al.[53] tested for potential irritancy the aerosol of a $C_{12}AE_9$-containing cream contraceptive; they applied this to the penile epidermis of 15 volunteers for 6–8 h for four consecutive days, stopped for four days, and then applied it for four more days. Two of the subjects showed slight erythema following two of the eight applications.

$C_{12}AE_9$, $C_{12}AE_{7.13}$, and $C_{12}AE_{11.9}$ have been employed to alleviate pain associated with peptic ulcers and gastritis.[57,58] Strack[59] administered $C_{12}AE_9$ (20 ml, 0.25%) orally to 44 patients 3–4 times/daily between meals for over four months. Pain was alleviated with no attendant side-effects. Hochrein and Schleicher[60] successfully treated 50 ulcer or gastritis patients with $C_{12}AE_9$ and noted

no intolerance. The $C_{12}AE_9$ had no effect on gastric secretion, circulation, or temperature. There was a decrease in bile synthesis and in gastric peristalsis.

Skin irritation and sensitization

Berberian et al.[53] tested aerosol preparations of creams containing 10%, 15%, or 20% $C_{12}AE_9$ on panelists (40 females and 13 males) applying 0.1 ml of sample to the arm three times per week for three weeks. Sixteen days later 0.05 ml challenge exposures were made. Repeated application of $C_{12}AE_9$ did not elicit hypersensitivity reactions.

Twelve panelists were exposed to $C_{12-15}AE_9$ (5%) or $C_{12-13}AE_{6.5}$ (5%) nine times in three weeks and then challenged two weeks later; for the former, no skin irritation resulted, while the latter produced minor irritation (one subject having developed slight erythema).[61]

Twelve subjects were exposed to $C_{14-15}AE_7$ (25% aqueous solution or undiluted) under occlusion for 4 h daily on three alternate days. Slight to negligible skin irritation developed.[27] When eight volunteers were exposed to $C_{12-13}AE_{6.5}$ (10% aqueous solution) for 24 h in an occluded patch test, minor skin irritation was observed.[27]

Some of the alcohol ethoxylates have local surface anesthetic and/or anti-itching properties. A variety of clinical studies have been reported for a mixture containing $C_{12}AE_{7.13}$ and $C_{12}AE_{11.9}$. The mixture (3 or 5%) was used to treat itching and pain experienced by 89 carcinoma patients who had x-ray induced skin reddening, eruption or ulceration. Both formulations were well-tolerated.[62] Aqueous solutions of the mixture (1–2 or 5%) were applied to five first-, 86 second-, and 12 third-degree burn patients to lessen the pain associated with their injuries. The solutions were found to have a local anesthetic effect for all but the first degree burn patients. No skin irritation or hypersensitivity was reported.[57]

Schultz[58] used aqueous solutions (1 or 2%) of the mixture described above on 63 patients with topical ulcers, second degree burns, surgical wounds, or interdigital mycoses and on 28 patients with pruritis. Of the 63 cases, there were five incidents of skin irritation but only in cases in which the skin was already inflamed. There was no irritation of intact skin.

A 2% aqueous solution of the mixture was applied to the oral mucosa of humans every day for eight weeks with no resulting irritation or sensitization.[58]

Schultz[58] and Schultz et al.[63] showed in ten volunteers that the analgesic effect of $C_{12}AE_9$ is potentiated 10 to 15-fold by the addition of 2.5 mg/dl of epinephrine or norepinephrine. No irritation or sensitivity reactions were reported even after applications were repeated for two months.

SUMMARY

The Laneths are ethoxylated lanolin alcohols that may be acetylated. They are used in a wide variety of cosmetic products and may be applied to all areas of the skin on a daily basis over an extended period of time. Laneth-10 Acetate, -9 Acetate, -5, -16, and -25 are used in concentration ranges of $\leq$0.1–25%, >1–10%, >0.1–10%, $\leq$0.1–5%, and >0.1–10%, respectively.

Acute oral toxicity studies indicate that Laneth-10 Acetate is relatively nontoxic to the rat; acute dermal toxicity studies indicate that it is relatively nontoxic to the guinea pig. Topical application of the undiluted ingredient provided no evidence of dermal corrosion or irritation to the rabbit. Laneth-10 Acetate was found to be a mild, transient irritant to the rabbit's eye. In a repeated insult occluded patch test, a 50% aqueous dispersion of Laneth-10 Acetate was shown to be nonirritating and nonsensitizing to 50 subjects. A product containing 1% Laneth-10 Acetate was found to be nonirritating and nonsensitizing to 200 volunteers, but was a "fatiguing" agent in 6% of the subjects.

Laneth-9 Acetate is nontoxic when administered orally to the rat. In dermal irritation and corrosion tests in the rabbit, Laneth-9 Acetate was found to be nonirritating and noncorrosive. Ocular irritation studies indicate that 20 percent and undiluted Laneth-9 Acetate are mild, transient eye irritants. Repeated insult occluded patch tests on 50 subjects indicate that a 50% preparation of the ingredient is nonirritating and nonsensitizing to the human skin, but does have a mild "fatiguing" effect.

Acute oral toxicity studies in the rat indicate that Laneth-5 is relatively innocuous. This ingredient was found to be a nonirritant to a mild primary skin irritant and a noncorrosive agent in the rabbit.

Laneth-5 is a mild, transient ocular irritant to the rabbit's eye. A 50% preparation of Laneth-5 was a nonirritating and nonsensitizing agent to the skin of 50 subjects, but was a mild "fatiguing" agent.

Laneth-16 is slightly toxic when administered orally to the rat. In the rabbit the undiluted ingredient is a mild to moderate primary skin irritant and a noncorrosive agent. Laneth-16 is a mild, transient eye irritant in the rabbit. Lanreth-16 has been added to shampoo preparations with known potential for ocular irritation specifically to reduce that irritancy. A 50% preparation of Laneth-16 was not a skin irritant or sensitizing agent in 50 volunteers, though it was a mild "fatiguing" agent in one of the subjects. In clinical studies a shampoo formulation containing 3.5 percent Laneth-16 was found to reduce ocular irritation when compared with the same formulation without Laneth-16.

The acute oral LD50 for 50% Laneth-25 was found to be in excess of 3.0 g/kg for the rat. A 10% preparation of Laneth-25 is not irritating to the rabbit skin. The undiluted ingredient is a minimal eye and severe skin irritant to the rabbit. There were no dermal corrosion tests. A 50% preparation of Laneth-25 was found to be nonirritating, "nonfatiguing," and nonsensitizing in 50 subjects.

No carcinogenicity or phototesting data on the Laneths were reported.

The alcohol ethoxylates are compounds closely related to the Laneths. Their PEG metabolities are noncarcinogenic and relatively innocuous when given orally. Various AE preparations are nontoxic when inhaled and do not inhibit ciliary movement in vitro. AEs are relatively innocuous when administered per os acutely and subchronically. AEs are not mucosal irritants. Some of the AEs are slight to moderate skin irritants but are not sensitizers. AEs tested in teratology, multiple generation, and mutagenesis studies presented no adverse effects.

CONCLUSION

On the basis of the available animal data and limited human experience presented in this report, the Panel concludes that Laneth-5, -16, -25, -9 Acetate, and -10 Acetate are safe for topical application to humans in the present practices of use and concentration.

REFERENCES

1. CIR. (1980). Safety assessment for acetylated lanolin alcohol and related ingredients. J. Environ. Pathol. Toxicol, Vol. 4, No. 4, Oct., 1980.
2. CHEMTOB, C., FAWAZ, F., and PUISIEUX, F. (1974). Analysis of ointments, oils and waxes. XVIII. Study of the chemical composition of liquid lanolin. 2. Study of alcohols. Ann. Pharm. Fr. **32**(7-8), 433-41.
3. FAWAZ, F., CHAIGNEAU, M., and PUISIEUX, F. (1973). Analysis of ointments, oils, and waxes. XIII. Composition of lanolin. 2. Study of the nonhyroxylated acids of total lanolin and its various fractions. Ann. Pharm. Fr. **31**(3), 217-26.
4. FAWAZ, F., CHAIGNEAU, M., and PUISIEUX, F. (1974). Analysis of ointments, oils and waxes. XVI. Chemical composition of lanolin. 5. Study of sterols and triterpene alcohols of total lanolin and of its various fractions. Ann. Pharm. Fr. **32**(5), 301-8.
5. FAWAZ, F., CHAIGNEAU, M., PUISIEUX, F., GIRY, L., and RICARD, L.P. (1974). Analysis of ointments, oils and waxes. XV. Chemical composition of lanolin. 4. Aliphatic alcohols of total lanolin and of its various fractions. Ann. Pharm. Fr. **32**(3-4), 215-25.
6. FAWAZ, F., MIET, C., and PUISIEUX, F. (1973). Analysis of ointments, oils and waxes. XII. Study of the chemical composition of wool fat (lanolin). 1. Preliminary examination and fractionation of a sample. Ann. Pharm. Fr. **31**(1), 63-72.
7. FAWAZ, F., MIET, C., and PUISIEUX, F. (1974). Analysis of ointments, oils and waxes. XIV. Composition of lanolin (wool fat). 3. Study of the hydroxylated acids of total lanolin and its various fractions. Ann. Pharm. Fr. **32**(1), 59-68.
8. CTFA. (1979). Submission of data by CTFA. CTFA Cosmetic Ingredient Chemical Descriptions for the Laneth-10 Acetate group.*

*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., NW, Washington, DC 20005.

9. ARTHUR D. LITTLE, INC. (1977). "Alcohol Ethoxylates". Human safety and environmental aspects of major surfactants. A Report to the Soap and Detergent Ass'n.
10. MORRISON, R.T. and BOYD, R.N. (1968). *Organic Chemistry*, 2nd ed. Boston, Mass: Allyn and Bacon, Inc., pp. 29, 889.
11. CONRAD, L.I. and MASO, H.F. (1962). Functional properties of lanolin derivatives in formulations. Amerchol, Sec. **1**(97), 1-8.
12. CTFA. (1979). Submission of data by CTFA. Summary of unpublished safety data for the Laneth-10 Acetate group.*
13. McCARTHY, J.P. and SCHLOSSMAN, M.L. (1975). Some properties of ethoxylated lanolin derivatives and their effects on cosmetic application. J. Soc. Cosmet. Chem. **26**(11), 523-30.
14. BARNETT, G. (1957). Lanolin derivatives and modifications. Drug Cosmet. Ind. **80**, 610-20.
15. CONRAD, L.I., MASO, H.F., and DERAGON, S.A. (1967). Influence of lanolin derivatives on dispersed systems. II. The dispersion of pigments in aqueous media. Am. Perfum. Cosmet.
16. CONRAD, L.I., MASO, H.F., and DERAGON, S.A. (1965). The influence of lanolin derivatives on dispersed systems. I. The dispersion of pigments in nonaqueous liquids. J. Soc. Cosmet. Chem. **16**, 617-36.
17. STUTSMAN, M.J. (1977). Analysis of hair fixative. *Newburger's Man. Cosmet. Anal.*, 2nd ed., pp. 72-7.
18. SUGAI, T. and HIGASHI, J. (1975). Hypersensitivity to hydrogenated lanolin. Contact Dermatitis **1**(3), 146-57.
19. GILLESPIE, D.T.C. (1948). Wool wax. A review of its properties, recovery and utilization. J. Text. Inst. **39**, 45.
20. SPILKER, C.W. and RICHEY, T.B. (1973). Analytical procedures for lanolin and lanolin derivatives. Cosmet. Perfum. **88**(9), 43-8.
21. EBLING, F.J. (1977). "Sebaceous Glands." Dermatotoxicology and Pharmacology. *Advances in Modern Toxicology*, vol. 4. F.N. Marzulli and H.I. Maibach, (eds.). New York: John Wiley and Sons. pp. 55-92.
22. BIRKEL, T.J., WARNER, C.R., and FAZIO, T. (1979). Gas chromatographic determination of 1, 4-dioxane in polysorbate 60 and polysorbate 80. J. Assoc. Offic. Anal. Chem. **62**, 931-6.
23. DERAGON, S.A. (1968). Enriching cosmetics with lanolin derivatives. Detergent Age.
24. FDA. (Aug. 31, 1976). Cosmetic product formulation data. Washington, DC. Food and Drug Administration.
25. DROTMAN, R.B. and DUPRE, G.D. (1976). Effects of long-term feeding of alkyl polyethoxylates on the metabolism of an alkyl polyethoxylate. Toxicol. Appl. Pharmacol. **37**(1), 138.
26. DROTMAN, R.B. (1980). The absorption, distribution, and excretion of alkylpolyethoxylates by rats and humans. Toxicol. Appl. Pharmacol. **52**(1), 38-44.
27. BENKE, G.M., BROWN, N.M., WALSH, M.J., and DROTMAN, R.B. (1977). Safety testing of alkyl polyethoxylate nonionic surfactants. I. Acute effects. Food Cosmet. Toxicol. **15**, 309-18.
28. PROCTER and GAMBLE CO. (1977). Unpublished data, in: *Surfactant Safety Report.*
29. SOEHRING, K., FRAHM, M., and MLETZKO, K. (1952). Contributions to the pharmacology of the alkyl derivatives of poly(ethylene oxide). IV. Local analgesic effects and comments on the comparative evaluation of conductivity-inhibiting substances. Arch. Int. Pharmacodyn. **91**, 112-30.
30. ZIPF, H.F. and DITTMANN, E.C. (1964). Relationships between alkyl chain length, lipophilicity, and local anesthetic and endoanesthetic activity in homologous alkyl polyglycol ethers. Naunyn-Schmeidelbergs Arch. Exp. Pathol. Paramakol. **247**, 544-57.
31. STELLMACH, R., SCHRODER, E., and SOEHRING, K. (1952). Concerning the measurement of analgesic effects in animal experiments. III. Quantitative evaluation of local analgetics on the skull of the dog. Arch. Int. Pharmacodyn. **89**(4), 380-98.
32. FREY, H.H. (1962). On the anticonvulsant activity of local anesthetics. Acta. Pharmacol. Toxicol. **19**, 205-11.
33. KONDO, T. and TOMIZAWA, M. (1968). Hemolysis by nonionic surface-active agents. J. Pharm. Sci. **57**, 1246-8.
34. SOEHRING, K. and NASEMANN, T. (1952). Contribution on the pharmacology of alkyl polyethylene oxide derivatives. III. Clotting time with repeated applications; hemolytic effects. Arch. Int. Pharmacodyn. **91**(12), 96-102.
35. PETER, C., SCHROPL, I., and FRANZWA, H. (1969). Experimentelle Untersuchunger uber die allergene Wirkung von Wollwachsachsalkoholen. Hautarzt **20**, 450-5.
36. NORTH AMERICAN CONTACT DERMATITIS GROUP (NACDG). (1979). Allergic indices for July 1, 1978 to June 30, 1979.
37. CLARK, E.W. (1975). Estimation of the general incidence of specific lanolin allergy. J. Soc. Cosmet.

Chem. **26**(7), 323–35.
38. CLARK, E.W., CRONIN, E., and WILKINSON, D.S. (1977). Lanolin with reduced sensitizing potential. A preliminary note. Contact Dermatitis **3**(2), 69–74.
39. AMERCHOL CORP. (1976). Submission of data by CTFA. Unpublished safety data on the Laneth-10 Acetate group.*
40. AVON CORP. (1974). Submission of data by CTFA. Unpublished safety data on the Laneth-10 Acetate group.*
41. CRODA, INC. (1976). Submission of data by CTFA. Unpublished safety data on the Laneth-10 Acetate group.*
42. MALMSTROM CHEMICAL CORP. (1972). Submission of data by CTFA. Unpublished safety data on the Laneth-10 Acetate group.*
43. FINKELSTEIN, P., LADEN, K., and MIECHOWSKI, W. (1965). Laboratory methods for evaluating skin irritancy. Toxicol. Appl. Pharmacol. **7**, 74–8.
44. CTFA. (1973). Submission of data by CTFA. Unpublished safety data on cosmetic product. Facial Mask No. 60518-A-1.*
45. SCHEUPLEIN, R.J. and BLANK, I.H. (1971). Permeability of the skin. Physiol. Rev. **51**(4), 702–47.
46. RUSSELL, K.L. and HOCH, S.G. (May, 1962). Product development and rabbit eye irritation. Proceedings of the Scientific Sec. of the Toilet Goods Ass'n., No. 37.
47. HOCH, S.G. and RUSSELL, K.L. (Dec. 1962). Effects of lanolin and derivatives on detergent solutions. The Toilet Goods Ass'n., No. 38.
48. HOCH, S.G., and RUSSELL, K.L. (1964). Low eye irritation shampoos. The Toilet Goods Ass'n., No. 42.
49. PUBLIC HEALTH SERVICE (PHS). (1975). Survey of compounds which have been tested for carcinogenic activity. PHS Publ. No. 1 149 (1951), Suppl. 1 (1957), Suppl. 2 (1969), 1961–67 vol. (1973), 1968–69 vol. (1972), 1970–71 vol. (1973), and 1972–73 vol. (1975).
50. GRUBB, T.C., DICK, L.C., and OSER, M. (1960). Studies on the toxicity of polyoxyethylene dodecanol. Toxicol. Appl. Pharmacol. **2**, 133–43.
51. SOEHRING, K., SCRIBA, K., FRAHM, M., and ZOELLNER, G. (1951). Contributions to the pharmacology of alkyl polyethylene oxide derivatives. I. Investigations of the acute and subchronic toxicity in various types of animals. Arch. Int. Pharmacodyn. **87**(3), 301–20.
52. BERBERIAN, D.A., GORMAN, W.G., DROBECK, H.P., COULSTON, F., and SLIGHTER, Jr., R.G. (1965). The toxicology and biological properties of Laureth-9 (a polyoxyethylene lauryl ether), a new spermicidal agent. Toxicol. Appl. Pharmacol. **7**, 206–14.
53. BERBERIAN, D.A., GORMAN, W.G., DROBECK, H.P., COULSTON, F., and SLIGHTER, Jr., R.G. (1965). Toxicology and spermicidal activity of a new contraceptive cream containing chlorindanol and Laureth-9. Toxicol. Appl. Pharmacol. **7**, 215–26.
54. MIMA, H., YASHIKI, T., NAKATINI, H., SHINTANI, S., and USUI, T. (1962). Studies on pharmaceutical preparations. XIII. Irritating action of aqueous injection of nonionic surface active agents. Yakugaku Zasshi **82**, 11771–6.
55. HARVEY, C., and STUCKEY, R.E. (1962). Spermicidal activity of surface-active agents. J. Reprod. Fertil. **2**, 124–31.
56. LARKIN, V.P. (1957). Polyoxyethylene dodecanol vaporization in the treatment of respiratory infections of infants and children. NY State J. Med. **57**(2), 2667–72.
57. HEYMAN, J. (1954). Local pain alleviation in burns. Med. Klinik. **49**, 559–60.
58. SCHULZ, K.H. (1952). On the use of alkyl-polyethylene oxide derivatives as surface anesthetics. Dermatol. Wochenschr. **126**(28), 657–62.
59. STRACK, K. (1950). On the treatment of peptic ulcers and gastritis with mucous membrane anesthesizing substances. Muench. Med. Wschr. No. 21–22.
60. HOCHREIN, M. and SCHLEICHER, I. (1951). Circulatory disturbances as the basis for pathogenesis and therapy of peptic ulcer. Deut. Med. Wschr. **76**(29–30), 936–9.
61. SHELL CHEMICAL CO. (1977). Unpublished data, in: *Surfactant Safety Report.*
62. BLASIU, A.P. (1953). Experiences with Thesit in x-ray dermatitis. Strahlentherapie **92**(1), 75–9.
63. SCHULZ, K.H., HARZ, A., and SOEHRING, K. (1952). Alkyl-polyethylene oxide ethers as local analgesics. Enhancement of effects in guinea pigs and man by addition of adrenaline and arterenol. Klin. Wocheschr. **30**(27–8), 663–4.
64. FASSET, D.W. and IRISH, D.D. (ed.). (1963). Industrial Hygiene and Toxicology. Vol. II, *Toxicology,* 2nd ed., rev., New York: Interscience Publishers. p. 1512.